Appendix A:

Pages 1130-1133 and 1635-1637 of
Physicians' Desk Reference, 53rd Edition, 1999

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

www.pdr.net

PHYSICIANS' DESK REFERENCE®

PDR®

53 EDITION

1999

PHYSICIANS' DESK REFERENCE®

M dical Consultant

Ronald Arky, MD, Charles S. Davidson Professor of Medicine and Master, Francis Weld Peabody Society, Harvard Medical School

Vice President of Directory Services: Stephen B. Greenberg

Director of Product Management: David P. Reiss
Senior Product Manager: Mark A. Friedman
Associate Product Manager: Bill Shaughnessy
Director of Sales: Dikran N. Barsamian
National Sales Manager: Anthony Sorce
National Account Manager: Don Bruccoleri
Account Managers:
Marion Gray, RPh
Lawrence C. Keary
Jeffrey F. Pfohl
Christopher N. Schmidt
Stephen M. Silverberg
Suzanne E. Yarrow, RN
National Sales Manager, Trade Group: Bill Gaffney
Director of Direct Marketing: Michael Bennett
Direct Marketing Manager: Lorraine M. Loening
Promotion Manager: Donna R. Lynn
Director, Professional Support Services: Mukesh Mehta, RPh

Senior Drug Information Specialist: Thomas Fleming, RPh
Drug Information Specialist: Maria Deutsch, MS, RPh, CDE
Editor, Special Projects: David W. Sifton
Vice President of Production: David A. Pitler
Director of Print Purchasing: Marjorie A. Duffy
Director of Operations: Carrie Williams
Manager of Production: Kimberly H. Vivas
Senior Production Coordinators: Amy B. Brooks, Dawn McCall
Production Coordinator: Mary Ellen R. Breun
PDR Data Manager: Jeffrey D. Schaefer
Senior Format Editor: Gregory J. Westley
Index Editors: Johanna M. Mazur, Robert N. Woerner
Art Associate: Joan K. Akerlind
Senior Digital Imaging Coordinator: Shawn W. Cahill
Digital Imaging Coordinator: Frank J. McElroy, III
Electronic Publishing Designer: Robert K. Grossman
Fulfillment Managers: Stephanie DeNardi, Kenneth Siebert

Officers of Medical Economics Company: *President and Chief Executive Officer:* Curtis B. Allen; *Vice President, New Media:* L. Suzanne BeDell; *Vice President, Corporate Human Resources:* Pamela M. Bilash; *Vice President and Chief Information Officer:* Steven M. Bressler; *Senior Vice President, Finance, and Chief Financial Officer:* Thomas W. Ehardt; *Vice President, Directory Services:* Stephen B. Greenberg; *Vice President, New Business Planning:* Linda G. Hope; *Executive Vice President, Healthcare Publishing and Communications:* Thomas J. Kelly; *Executive Vice President, Magazine Publishing:* Lee A. Maniscalco; *Vice President, Group Publisher:* Terrence W. Meacock; *Vice President, Production:* David A. Pitler; *Vice President, Group Publisher:* Thomas C. Pizor; *Vice President, Magazine Business Management:* Eric Schlett; *Senior Vice President, Operations:* John R. Ware

Printed on recycled paper

ISBN: 1-56363-288-8

Flovent Rotadisk—Cont.

Respiratory: Asthma exacerbation, bronchospasm, chest tightness, dyspnea, paradoxical bronchospasm, and wheezing.

Skin: Contusions, ecchymoses, and pruritus.

OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS). Inhalation by healthy volunteers of a single dose of 4000 mcg of fluticasone propionate inhalation powder or single doses of 1760 or 3520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of 1320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. The oral and subcutaneous median lethal doses in mice and rats were >1000 mg/kg (>2000 and >4100 times, respectively, the maximum recommended daily inhalation dose in adults and >9600 and >19 000 times, respectively, the maximum recommended daily inhalation dose in children on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION

FLOVENT ROTADISK should be administered by the orally inhaled route in patients 4 years of age and older. Individual patients will experience a variable time to onset and degree of symptom relief. Generally, fluticasone propionate inhalation powder has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhaled administration of fluticasone propionate can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment.

After asthma stability has been achieved, it is always desirable to titrate to the lowest effective dose to reduce the possibility of side effects. Doses as low as 50 mcg twice daily have been shown to be effective in some patients. For patients who do not respond adequately to the starting dose after 2 weeks of therapy, higher doses may provide additional asthma control. The safety and efficacy of FLOVENT ROTADISK when administered in excess of recommended doses have not been established.

Rinsing the mouth after inhalation is advised.

The recommended starting dose and the highest recommended dose of fluticasone propionate inhalation powder, based on prior anti-asthma therapy, are listed in the following table.

[See second table at top of previous page]

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with fluticasone propionate inhalation powder, efficacy and safety did not differ from that in younger patients. Consequently, no dosage adjustment is recommended.

Directions for Use: Illustrated Patient's Instructions for Use accompany each package of FLOVENT ROTADISK.

HOW SUPPLIED

FLOVENT ROTADISK 50 mcg is a circular double-foil pack containing four blisters of the drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and the tube is packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the foil pouch of 15 ROTADISKS and one dark orange- and peach-colored DISKHALER inhalation device (NDC 0173-0511-00).

FLOVENT ROTADISK 100 mcg is a circular double-foil pack containing four blisters of the drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and the tube is packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the foil pouch of 15 ROTADISKS and one dark orange- and peach-colored DISKHALER inhalation device (NDC 0173-0509-00).

FLOVENT ROTADISK 250 mcg is a circular double-foil pack containing four blisters of the drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and the tube is packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the foil pouch of 15 ROTADISKS and one dark orange- and peach-colored DISKHALER inhalation device (NDC 0173-0504-00).

Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place. Keep out of reach of children. Use the ROTADISK blisters within 2 months after opening of the moisture-protective foil overwrap or before the expiration date, whichever comes first. Do not puncture any fluticasone propionate ROTADISK blister until taking a dose using the DISKHALER.

November 1997/RL-472

Shown in Product Identification Guide, page 312

FORTAZ ℞

[for' taz]

(ceftazidime for injection)

FORTAZ ℞

(ceftazidime sodium injection)

For Intravenous or Intramuscular Use

DESCRIPTION

Ceftazidime is a semisynthetic, broad-spectrum, beta-lactam antibiotic for parenteral administration. It is the pentahydrate of pyridinium, 1-[[7-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy) imino]acetyl] amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6R-[6α,7β(Z)]].

The empirical formula is $C_{22}H_{32}N_6O_{12}S_2$, representing a molecular weight of 636.6.

FORTAZ is a sterile, dry powdered mixture of ceftazidime pentahydrate and sodium carbonate. The sodium carbonate at a concentration of 118 mg/g of ceftazidime activity has been admixed to facilitate dissolution. The total sodium content of the mixture is approximately 54 mg (2.3 mEq)/g of ceftazidime activity.

FORTAZ in sterile crystalline form is supplied in vials equivalent to 500 mg, 1 g, 2 g, or 6 g of anhydrous ceftazidime and in ADD-Vantage® vials equivalent to 1 or 2 g of anhydrous ceftazidime. Solutions of FORTAZ range in color from light yellow to amber, depending on the diluent and volume used. The pH of freshly constituted solutions usually ranges from 5 to 8.

FORTAZ is available as a frozen, iso-osmotic, sterile, nonpyrogenic solution with 1 or 2 g of ceftazidime as ceftazidime sodium premixed with approximately 2.2 or 1.6 g, respectively, of dextrose hydrous, USP. Dextrose has been added to adjust the osmolality. Sodium hydroxide is used to adjust pH and neutralize ceftazidime pentahydrate free acid to the sodium salt. The pH may have been adjusted with hydrochloric acid. Solutions of premixed FORTAZ range in color from light yellow to amber. The solution is intended for intravenous (IV) use after thawing to room temperature. The osmolality of the solution is approximately 300 mOsmol/kg, and the pH of thawed solutions ranges from 5 to 7.5.

The plastic container for the frozen solution is fabricated from a specially designed multilayer plastic, PL 2040. Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

After IV administration of 500-mg and 1-g doses of ceftazidime over 5 minutes to normal adult male volunteers, mean peak serum concentrations of 45 and 90 mcg/mL, respectively, were achieved. After IV infusion of 500-mg, 1-g, and 2-g doses of ceftazidime over 20 to 30 minutes to normal adult male volunteers, mean peak serum concentrations of 42, 69, and 170 mcg/mL, respectively, were achieved. The average serum concentrations following IV infusion of 500-mg, 1-g, and 2-g doses to these volunteers over an 8-hour interval are given in Table 1.

Table 1

Ceftazidime IV Dose	Serum Concentrations (mcg/mL) 0.5 h	1 h	2 h	4 h	8 h
500 mg	42	25	12	6	2
1 g	60	39	23	11	3
2 g	129	75	42	13	5

The absorption and elimination of ceftazidime were directly proportional to the size of the dose. The half-life following IV administration was approximately 1.9 hours. Less than 10% of ceftazidime was protein bound. The degree of protein binding was independent of concentration. There was no evidence of accumulation of ceftazidime in the serum in individuals with normal renal function following multiple IV doses of 1 and 2 g every 8 hours for 10 days.

Following intramuscular (IM) administration of 500-mg and 1-g doses of ceftazidime to normal adult volunteers, the mean peak serum concentrations were 17 and 39 mcg/mL, respectively, at approximately 1 hour. Serum concentrations remained above 4 mcg/mL for 6 and 8 hours after the IM administration of 500-mg and 1-g doses, respectively. The half-life of ceftazidime in these volunteers was approximately 2 hours.

The presence of hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g intravenously every 8 hours for 5 days. Therefore, a dosage adjustment from the normal recommended dosage is not required for patients with hepatic dysfunction, provided renal function is not impaired.

Approximately 80% to 90% of an IM or IV dose of ceftazidime is excreted unchanged by the kidneys over a 24-hour period. After the IV administration of single 500-mg doses, approximately 50% of the dose appeared in the urine in the first 2 hours. An additional 20% was excreted between 2 and 4 hours after dosing, and approximately another 12% of the dose appeared in the urine between 4 and 8 hours later. The elimination of ceftazidime by the kidneys resulted in high therapeutic concentrations in the urine. The mean renal clearance of ceftazidime was approximately 100 mL/min. The calculated plasma clearance of approximately 115 mL/min indicated nearly complete elimination of ceftazidime by the renal route. Administration of probenecid before dosing had no effect on the elimination half-life of ceftazidime. This suggested that ceftazidime is eliminated by glomerular filtration and is not actively secreted by renal tubular mechanisms.

Since ceftazidime is eliminated almost solely by the kidneys, its serum half-life is significantly prolonged in patients with impaired renal function. Consequently, dosage adjustments in such patients as described in the DOSAGE AND ADMINISTRATION section are suggested.

Therapeutic concentrations of ceftazidime are achieved in the following body tissues and fluids.

[See table 2 at top of next page]

Microbiology: Ceftazidime is bactericidal in action, exerting its effect by inhibition of enzymes responsible for cell wall synthesis. A wide range of gram-negative organisms are susceptible to ceftazidime *in vitro*, including strains resistant to gentamicin and other aminoglycosides. In addition, ceftazidime has been shown to be active against many gram-positive organisms. It is highly stable to most clinically important beta-lactamases, plasmid or chromosomal, which are produced by both gram-negative and gram-positive organisms and, consequently, is active against many strains resistant to ampicillin and other cephalosporins.

Ceftazidime has been shown to be active against the following organisms both *in vitro* and in clinical infections (see INDICATIONS AND USAGE):

Aerobes, Gram-negative: *Citrobacter* spp., including *Citrobacter freundii* and *Citrobacter diversus*; *Enterobacter* spp., including *Enterobacter cloacae* and *Enterobacter aerogenes; Escherichia coli; Haemophilus influenzae*, including ampicillin-resistant strains; *Klebsiella* spp. (including *Klebsiella pneumoniae*); *Neisseria meningitidis; Proteus mirabilis; Proteus vulgaris; Pseudomonas* spp. (including *Pseudomonas aeruginosa*); and *Serratia* spp.

Aerobes, Gram-positive: *Staphylococcus aureus*, including penicillinase- and non–penicillinase-producing strains; *Streptococcus agalactiae* (group B streptococci), *Streptococcus pneumoniae*, and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

Anaerobes: *Bacteroides* spp. (NOTE: many strains of *Bacteroides fragilis* are resistant).

Ceftazidime has been shown to be active *in vitro* against most strains of the following organisms; however, the clinical significance of these data is unknown: *Acinetobacter* spp., *Clostridium* spp. (not including *Clostridium difficile*), *Haemophilus parainfluenzae, Morganella morganii* (formerly *Proteus morganii*), *Neisseria gonorrhoeae, Proteus* spp., *Peptostreptococcus* spp., *Providencia* spp. [including *Providencia rettgeri*, formerly *Proteus rettgeri*), *Salmonella* spp., *Shigella* spp., *Staphylococcus epidermidis*, and *Yersinia enterocolitica*.

Ceftazidime and the aminoglycosides have been shown to be synergistic *in vitro* against *Pseudomonas aeruginosa* and the enterobacteriaceae. Ceftazidime and carbenicillin have also been shown to be synergistic *in vitro* against *Pseudomonas aeruginosa*.

Ceftazidime is not active *in vitro* against methicillin-resistant staphylococci, *Streptococcus faecalis* and many other enterococci, *Listeria monocytogenes, Campylobacter* spp., and *Clostridium difficile*.

Susceptibility Tests: ***Diffusion Techniques:*** Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such procedure[1-3] has been recommended for use with disks to test susceptibility to ceftazidime.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30-mcg ceftazidime disk should be interpreted according to the following criteria:

Susceptible organisms produce zones of 18 mm or greater, indicating that the test organism is likely to respond to therapy.

Organisms that produce zones of 15 to 17 mm are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

Organisms should be tested with the ceftazidime disk. Ceftazidime has been shown by *in vitro* tests to be active against certain strains found resistant when other beta-lactam disks are used.

...ardized procedures require the use of laboratory control organisms. The 30-mcg ceftazidime disk should give ... diameters between 25 and 32 mm for *Escherichia coli* ... 25922. For *Pseudomonas aeruginosa* ATCC 27853, ... zone diameters should be between 22 and 29 mm. For ...*ylococcus aureus* ATCC 25923, the zone diameters ... be between 16 and 20 mm.

...Techniques: In other susceptibility testing procedures, e.g., ICS agar dilution or the equivalent, a bacterial ... may be considered susceptible if the minimum inhibitory concentration (MIC) value for ceftazidime is not more than 16 mcg/mL. Organisms are considered resistant to ceftazidime if the MIC is ≥ 64 mcg/mL. Organisms having a MIC value of < 64 mcg/mL but > 16 mcg/mL are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

With standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard ceftazidime powder should give MIC values in the range of 4 to 16 mcg/mL for *Staphylococcus aureus* ATCC 25923. For *Escherichia coli* ATCC 25922, the MIC range should be between 0.125 and 0.5 mcg/mL. For *Pseudomonas aeruginosa* ATCC 27853, the MIC range should be between 0.5 and 2 mcg/mL.

...CATIONS AND USAGE

...TAZ is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

...Respiratory Tract Infections, including pneumonia caused by *Pseudomonas aeruginosa* and other *Pseudomonas* spp., *Haemophilus influenzae,* including ampicillin-resistant strains; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus mirabilis; Escherichia coli; Serratia* spp.; *Citrobacter* spp.; *Streptococcus pneumoniae,* and *Staphylococcus aureus* (methicillin-susceptible strains).

... and Skin-Structure Infections caused by *Pseudomonas aeruginosa; Klebsiella* spp.; *Escherichia coli; Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus; Enterobacter* spp.; *Serratia* spp.; *Staphylococcus aureus* (methicillin-susceptible strains); and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

...ary Tract Infections, both complicated and uncomplicated, caused by *Pseudomonas aeruginosa; Enterobacter* spp.; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus; Klebsiella* spp.; and *Escherichia coli.*

...erial Septicemia caused by *Pseudomonas aeruginosa, Klebsiella* spp., *Haemophilus influenzae, Escherichia coli, Serratia* spp., *Streptococcus pneumoniae,* and *Staphylococcus aureus* (methicillin-susceptible strains).

... and Joint Infections caused by *Pseudomonas aeruginosa, Klebsiella* spp., *Enterobacter* spp., and *Staphylococcus aureus* (methicillin-susceptible strains).

...ecologic Infections, including endometritis, pelvic ...litis, and other infections of the female genital tract caused by *Escherichia coli.*

...-abdominal Infections, including peritonitis caused by *Escherichia coli, Klebsiella* spp., and *Staphylococcus aureus* (methicillin-susceptible strains) and polymicrobial infections caused by aerobic and anaerobic organisms and *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).

... Nervous System Infections, including meningitis caused by *Haemophilus influenzae* and *Neisseria meningitidis.* Ceftazidime has also been used successfully in a limited number of cases of meningitis due to *Pseudomonas aeruginosa* and *Streptococcus pneumoniae.*

...ns for bacterial cultures should be obtained before ... in order to isolate and identify causative organisms ... determine their susceptibility to ceftazidime. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, antibiotic treatment should be adjusted accordingly.

...TAZ may be used alone in cases of confirmed or suspected sepsis. Ceftazidime has been used successfully in clinical trials as empiric therapy in cases where various conventional therapies with other antibiotics have been used.

...TAZ may also be used concomitantly with other antibiotics such as aminoglycosides, vancomycin, and clindamycin in severe and life-threatening infections, and in the immunocompromised patient. When such concomitant treatment is appropriate, prescribing information in the labeling for other antibiotics should be followed. The dose depends on the severity of the infection and the patient's condition.

...TRAINDICATIONS

...TAZ is contraindicated in patients who have shown hypersensitivity to ceftazidime or the cephalosporin group of antibiotics.

...INGS

...RE THERAPY WITH FORTAZ IS INSTITUTED, ...FUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTAZIDIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO FORTAZ OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftazidime, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Elevated levels of ceftazidime in patients with renal insufficiency can lead to seizures, encephalopathy, asterixis, and neuromuscular excitability (see PRECAUTIONS).

PRECAUTIONS

General: Ceftazidime has not been shown to be nephrotoxic; however, high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with transient or persistent reduction of urinary output because of renal insufficiency. The total daily dosage should be reduced when ceftazidime is administered to patients with renal insufficiency (see DOSAGE AND ADMINISTRATION). Elevated levels of ceftazidime in these patients can lead to seizures, encephalopathy, asterixis, and neuromuscular excitability. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms.

As with other antibiotics, prolonged use of FORTAZ may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Inducible type I beta-lactamase resistance has been noted with some organisms (e.g., *Enterobacter* spp., *Pseudomonas* spp., and *Serratia* spp.). As with other extended-spectrum beta-lactam antibiotics, resistance can develop during therapy, leading to clinical failure in some cases. When treating infections caused by these organisms, periodic susceptibility testing should be performed when clinically appropriate. If patients fail to respond to monotherapy, an aminoglycoside or similar agent should be considered.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal and hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

FORTAZ should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Distal necrosis can occur after inadvertent intra-arterial administration of ceftazidime.

Drug Interactions: Nephrotoxicity has been reported following concomitant administration of cephalosporins with aminoglycoside antibiotics or potent diuretics such as furosemide. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Nephrotoxicity and ototoxicity were not noted when ceftazidime was given alone in clinical trials.

Chloramphenicol has been shown to be antagonistic to beta-lactam antibiotics, including ceftazidime, based on *in vitro* studies and time kill curves with enteric gram-negative bacilli. Due to the possibility of antagonism *in vivo,* particularly when bactericidal activity is desired, this drug combination should be avoided.

Drug/Laboratory Test Interactions: The administration of ceftazidime may result in a false-positive reaction for glucose in the urine using CLINITEST® tablets, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX® or TES-TAPE®) be used.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. However, a mouse Micronucleus test and an Ames test were both negative for mutagenic effects.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in mice and rats at doses up to 40 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to FORTAZ. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Ceftazidime is excreted in human milk in low concentrations. Caution should be exercised when FORTAZ is administered to a nursing woman.

Pediatric Use: (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Ceftazidime is generally well tolerated. The incidence of adverse reactions associated with the administration of ceftazidime was low in clinical trials. The most common were local reactions following IV injection and allergic and gastrointestinal reactions. Other adverse reactions were encountered infrequently. No disulfiramlike reactions were reported.

The following adverse effects from clinical trials were considered to be either related to ceftazidime therapy or were of uncertain etiology:

Local Effects, reported in fewer than 2% of patients, were phlebitis and inflammation at the site of injection (1 in 69 patients).

Continued on next page

Table 2: Ceftazidime Concentrations in Body Tissues and Fluids

Tissue or Fluid	Dose/ Route	No. of Patients	Time of Sample Postdose	Average Tissue or Fluid Level (mcg/mL or mcg/g)
Urine	500 mg IM	6	0–2 h	2,100.0
	2 g IV	6	0–2 h	12,000.0
Bile	2 g IV	3	90 min	36.4
Synovial fluid	2 g IV	13	2 h	25.6
Peritoneal fluid	2 g IV	8	2 h	48.6
Sputum	1 g IV	8	1 h	9.0
Cerebrospinal fluid	2 g q8h IV	5	120 min	9.8
(inflamed meninges)	2 g q8h IV	6	180 min	9.4
Aqueous humor	2 g IV	13	1–3 h	11.0
Blister fluid	1 g IV	7	2–3 h	19.7
Lymphatic fluid	1 g IV	7	2–3 h	23.4
Bone	2 g IV	8	0.67 h	31.1
Heart muscle	2 g IV	35	30–280 min	12.7
Skin	2 g IV	22	30–180 min	6.6
Skeletal muscle	2 g IV	35	30–280 min	9.4
Myometrium	2 g IV	31	1–2 h	18.7

This product information is based on labeling in effect on June 1, 1998. For further information, contact via direct mail, phone, or web site Medical Information: Glaxo Wellcome Inc., PO Box 13398, Research Triangle Park, NC 27709. Healthcare Professionals (Medical Information): 800-334-0089 Patients (Customer Response Center): 888-TALK2GW (1-888-825-5249) Glaxo Wellcome Corporate Web Site: www.glaxowellcome.com

Fortaz—C nt.

Hypersensitivity Reactions, reported in 2% of patients, were pruritus, rash, and fever. Immediate reactions, generally manifested by rash and/or pruritus, occurred in 1 in 285 patients. Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have also been reported with cephalosporin antibiotics, including ceftazidime. Angioedema and anaphylaxis (bronchospasm and/or hypotension) have been reported very rarely.

Gastrointestinal Symptoms, reported in fewer than 2% of patients, were diarrhea (1 in 78), nausea (1 in 156), vomiting (1 in 500), and abdominal pain (1 in 416). The onset of pseudomembranous colitis symptoms may occur during or after treatment (see WARNINGS).

Central Nervous System Reactions (fewer than 1%) included headache, dizziness, and paresthesia. Seizures have been reported with several cephalosporins, including ceftazidime. In addition, encephalopathy, asterixis, and neuromuscular excitability have been reported in renally impaired patients treated with unadjusted dosing regimens of ceftazidime (see PRECAUTIONS: General).

Less Frequent Adverse Events (fewer than 1%) were candidiasis (including oral thrush) and vaginitis.

Hematologic: Rare cases of hemolytic anemia have been reported.

Laboratory Test Changes noted during FORTAZ clinical trials were transient and included eosinophilia (1 in 13), positive Coombs' test without hemolysis (1 in 23), thrombocytosis (1 in 45), and slight elevations in one or more of the hepatic enzymes, aspartate aminotransferase (AST, SGOT) (1 in 16), alanine aminotransferase (ALT, SGPT) (1 in 15), LDH (1 in 18), GGT (1 in 19), and alkaline phosphatase (1 in 23). As with some other cephalosporins, transient elevations of blood urea, blood urea nitrogen, and/or serum creatinine were observed occasionally. Transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia, and lymphocytosis were seen very rarely.

In addition to the adverse reactions listed above that have been observed in patients treated with ceftazidime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Urticaria, colitis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage.

Altered Laboratory Tests: Prolonged prothrombin time, false-positive test for urinary glucose, elevated bilirubin, pancytopenia.

OVERDOSAGE

Ceftazidime overdosage has occurred in patients with renal failure. Reactions have included seizure activity, encephalopathy, asterixis, and neuromuscular excitability. Patients who receive an acute overdosage should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis or peritoneal dialysis may aid in the removal of ceftazidime from the body.

DOSAGE AND ADMINISTRATION

Dosage: The usual adult dosage is 1 gram administered intravenously or intramuscularly every 8 to 12 hours. The dosage and route should be determined by the susceptibility of the causative organisms, the severity of infection, and the condition and renal function of the patient.

The guidelines for dosage of FORTAZ are listed in Table 3. The following dosage schedule is recommended.

[See table 3 below]

Impaired Hepatic Function: No adjustment in dosage is required for patients with hepatic dysfunction.

Impaired Renal Function: Ceftazidime is excreted by the kidneys, almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function (glomerular filtration rate [GFR] <50 mL/min), it is recommended that the dosage of ceftazidime be reduced to compensate for its slower excretion. In patients with suspected renal insufficiency, an initial loading dose of 1 gram of FORTAZ may be given. An estimate of GFR should be made to determine the appropriate maintenance dosage. The recommended dosage is presented in Table 4:

Table 4: Recommended Maintenance Dosages of FORTAZ in Renal Insufficiency

NOTE: IF THE DOSE RECOMMENDED IN TABLE 3 ABOVE IS LOWER THAN THAT RECOMMENDED FOR PATIENTS WITH RENAL INSUFFICIENCY, AS OUTLINED IN TABLE 4, THE LOWER DOSE SHOULD BE USED.

Creatinine Clearance (mL/min)	Recommended Unit Dose of FORTAZ	Frequency of Dosing
50–31	1 gram	q12h
30–16	1 gram	q24h
15–6	500 mg	q24h
<5	500 mg	q48h

When only serum creatinine is available, the following formula (Cockcroft's equation)† may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

Males:

$$\text{Creatinine clearance (ml/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.85 × male value

In patients with severe infections who would normally receive 6 grams of FORTAZ daily, were it not for renal insufficiency, the unit dose given in the table above may be increased by 50% or the dosing frequency may be increased appropriately. Further dosing should be determined by therapeutic monitoring, severity of the infection, and susceptibility of the causative organism.

In pediatric patients as for adults, the creatinine clearance should be adjusted for body surface area or lean body mass, and the dosing frequency should be reduced in cases of renal insufficiency.

In patients undergoing hemodialysis, a loading dose of 1 gram as recommended, followed by 1 gram after each hemodialysis period.

FORTAZ can also be used in patients undergoing intraperitoneal dialysis and continuous ambulatory peritoneal dialysis. In such patients, a loading dose of 1 gram of FORTAZ may be given, followed by 500 mg every 24 hours. In addition to IV use, FORTAZ can be incorporated in the dialysis fluid at a concentration of 250 mg for 2 L of dialysis fluid.

Table 3: Recommended Dosage Schedule

	Dose	Frequency
Adults		
Usual recommended dosage	1 gram IV or IM	q8–12h
Uncomplicated urinary tract infections	250 mg IV or IM	q12h
Bone and joint infections	2 grams IV	q12h
Complicated urinary tract infections	500 mg IV or IM	q8–12h
Uncomplicated pneumonia; mild skin and skin-structure infections	500 mg–1 gram IV or IM	q8h
Serious gynecologic and intra-abdominal infections	2 grams IV	q8h
Meningitis	2 grams IV	q8h
Very severe life-threatening infections, especially in immunocompromised patients	2 grams IV	q8h
Lung infections caused by *Pseudomonas* spp. in patients with cystic fibrosis with normal renal function*	30–50 mg/kg IV to a maximum of 6 grams per day	q8h
Neonates (0–4 weeks)	30 mg/kg IV	q12h
Infants and Children (1 month–12 years)	30–50 mg/kg IV to a maximum of 6 grams per day†	q8h

*Although clinical improvement has been shown, bacteriologic cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis.

†The higher dose should be reserved for immunocompromised pediatric patients or pediatric patients with cystic fibrosis or meningitis.

Note: Generally FORTAZ should be continued after the signs and symptoms of infection have but in complicated infections longer therapy quired.

Administration: FORTAZ may be given by deep IM injection into a large muscle mass upper outer quadrant of the gluteus maximus of the thigh. Intra-arterial administration avoided (see PRECAUTIONS).

Intramuscular Administration: For IM adm FORTAZ should be constituted with one of the luents: sterile water for injection, bacteriost injection, or 0.5% or 1% lidocaine hydrochlor Refer to Table 5.

Intravenous Administration: The IV route is patients with bacterial septicemia, bacterial peritonitis, or other severe or life-threatening for patients who may be poor risks because of tance resulting from such debilitating conditio trition, trauma, surgery, diabetes, heart failur nancy, particularly if shock is present or pendi

For direct intermittent IV administration FORTAZ as directed in Table 5 with sterile wa tion. Slowly inject directly into the vein over a p 5 minutes or give through the tubing of an ad set while the patient is also receiving one of the IV fluids (see COMPATIBILITY AND STABILITY

For IV infusion, constitute the 1- or 2-gram i with 100 mL of sterile water for injection or one patible IV fluids listed under the COMPATIBIL STABILITY section. Alternatively, constitute 1-gram or 2-gram vial and add an appropriate the resulting solution to an IV container with compatible IV fluids.

Intermittent IV infusion with a Y-type admin can be accomplished with compatible solutions during infusion of a solution containing ceftazidi sirable to discontinue the other solution.

ADD-Vantage vials are to be constituted only wit mL of 5% dextrose injection, 0.9% sodium chlori or 0.45% sodium chloride injection in Abbott ADD flexible diluent containers (see instructions for U section of the product package insert). ADD-Va that have been used in Abbott ADD-Vantage con tainers and activated to dissolve the drug are hours at room temperature or for 7 days under tion. Joined vials that have not been activated within a 14-day period; this period corresponds t use of Abbott ADD-Vantage containers following the outer packaging (overwrap).

Freezing solutions of FORTAZ in the ADD-Vanta is not recommended.

[See table 5 at top of next page]

All vials of FORTAZ as supplied are under red sure. When FORTAZ is dissolved, carbon dioxide and a positive pressure develops. For ease of use low the recommended techniques of constitution on the detachable instructions for Constitution the product package insert.

Solutions of FORTAZ, like those of most beta-l biotics, should not be added to solutions of amin antibiotics because of potential interaction. However, if concurrent therapy with FORTAZ and noglycoside is indicated, each of these antibiotics ministered separately to the same patient.

Directions for Use of FORTAZ Frozen in GALAXY Containers: FORTAZ, supplied as a frozen, ster motic, nonpyrogenic solution in plastic containers administered after thawing either as a continuous mittent IV infusion. The thawed solution is sta hours at room temperature or for 7 days if stored frigeration. Do not Refreeze.

Thaw container at room temperature (25°C) or un eration (5°C). Do not force thaw by immersion baths or by microwave irradiation. Components of tion may precipitate in the frozen state and will upon reaching room temperature with little or no Potency is not affected. Mix after solution has re temperature. Check for minute leaks by squee firmly. Discard bag if leaks are found as sterility paired. Do not add supplementary medication. D unless solution is clear and seal is intact. Use sterile equipment.

Caution: Do not use plastic containers in series tions. Such use could result in air embolism due air being drawn from the primary container before istration of the fluid from the secondary container plete.

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of
3. Attach administration set. Refer to complete accompanying set.

COMPATIBILITY AND STABILITY

Intramuscular: FORTAZ, when constituted as with sterile water for injection, bacteriostatic wat

Table 5: Preparation of FORTAZ Solutions

Size	Amount of Diluent to be Added (mL)	Approximate Available Volume (mL)	Approximate Ceftazidime Concentration (mg/mL)
Intramuscular			
500-mg vial	1.5	1.8	280
1-gram vial	3.0	3.6	280
Intravenous			
500-mg vial	5.0	5.3	100
1-gram vial	10.0	10.6	100
2-gram vial	10.0	11.5	170
Infusion pack			
1-gram vial	100 *	100	10
2-gram vial	100 *	100	20
Pharmacy bulk package			
6-gram vial	26	30	200

Note: Addition should be in two stages (see Instructions for Constitution accompanying the product package insert).

...tion, or 0.5% or 1% lidocaine hydrochloride injection, ...intains satisfactory potency for 24 hours at room temper... or for 7 days under refrigeration. Solutions in sterile ...er for injection that are frozen immediately after consti... in the original container are stable for 3 months ...n stored at −20°C. Once thawed, solutions should not ...refrozen. Thawed solutions may be stored for up to 8 ...s at room temperature or for 4 days in a refrigerator.

Intravenous: FORTAZ, when constituted as directed with ...rile water for injection, maintains satisfactory potency ...24 hours at room temperature or for 7 days under refrig... Solutions in sterile water for injection in the infu... vial or in 0.9% sodium chloride injection in VIAFLEX® ...all-volume containers that are frozen immediately after ...stitution are stable for 6 months when stored at −20°C. ...not force thaw by immersion in water baths or by micro... irradiation. Once thawed, solutions should not be re... Thawed solutions may be stored for up to 24 hours at ... temperature or for 7 days in a refrigerator. More con...trated solutions in sterile water for injection in the orig... container that are frozen immediately after constitu... are stable for 3 months when stored at −20°C. Once ...wed, solutions should not be refrozen. Thawed solutions ...y be stored for up to 8 hours at room temperature or for ...ays in a refrigerator.

FORTAZ is compatible with the more commonly used IV in... fluids. Solutions at concentrations between 1 and 40 ...mL in 0.9% sodium chloride injection; 1/6 M sodium lac... injection; 5% dextrose injection; 5% dextrose and ...2% sodium chloride injection; 5% dextrose and 0.45% ...ium chloride injection; 5% dextrose and 0.9% sodium ...oride injection; 10% dextrose injection; ringer's injection, ...'s lactated ringer's injection, USP; 10% invert sugar in ...er for injection; and NORMOSOL®-M in 5% dextrose in... may be stored for up to 24 hours at room tempera... or for 7 days if refrigerated.

...- and 2-g FORTAZ ADD-Vantage vials, when diluted ...0 or 100 mL of 5% dextrose injection, 0.9% sodium chlo... injection, or 0.45% sodium chloride injection, may be ...ed for up to 24 hours at room temperature or for 7 days ...r refrigeration.

FORTAZ is less stable in sodium bicarbonate injection than ...other IV fluids. It is not recommended as a diluent. Solu... of FORTAZ in 5% dextrose injection and 0.9% sodium ...oride injection are stable for at least 6 hours at room ...perature in plastic tubing, drip chambers, and volume ...rol devices of common IV infusion sets.

...azidime at a concentration of 4 mg/mL has been found ...patible for 24 hours at room temperature or for 7 days ...r refrigeration in 0.9% sodium chloride injection or 5% ...ose injection when admixed with: cefuroxime sodium ...ACEF®) 3 mg/mL; heparin 10 or 50 U/mL; or potas... chloride 10 or 40 mEq/L.

...omycin solution exhibits a physical incompatibility ...n mixed with a number of drugs, including ceftazidime. ...likelihood of precipitation with ceftazidime is depen... on the concentrations of vancomycin and ceftazidime ...nt. It is therefore recommended, when both drugs are ...administered by intermittent IV infusion, that they be ...separately, flushing the IV lines (with one of the com... IV fluids) between the administration of these two ...s.

Parenteral drug products should be inspected visu... for particulate matter before administration whenever ...n and container permit.

...th other cephalosporins, FORTAZ powder as well as ...ons tend to darken, depending on storage conditions; ...the stated recommendations, however, product po... is not adversely affected.

SUPPLIED

...AZ in the dry state should be stored between 15° and ...60° and 86°F) and protected from light. FORTAZ is a ...hite to off-white powder supplied in vials and infusion ...s as follows:

NDC 0173-0377-31	500-mg* Vial (Tray of 25)
NDC 0173-0378-35	1-g* Vial (Tray of 25)
NDC 0173-0379-34	2-g* Vial (Tray of 10)
NDC 0173-0380-32	1-g* Infusion Pack (Tray of 10)
NDC 0173-0381-32	2-g* Infusion Pack (Tray of 10)
NDC 0173-0382-37	6-g* Pharmacy Bulk Package (Tray of 6)
NDC 0173-0434-00	1-g ADD-Vantage® Vial (Tray of 25)
NDC 0173-0435-00	2-g ADD-Vantage® Vial (Tray of 10)

(The above ADD-Vantage vials are to be used only with Abbott ADD-Vantage diluent containers.)

FORTAZ frozen as a premixed solution of ceftazidime sodium should not be stored above −20° C. FORTAZ is supplied frozen in 50-mL, single-dose, plastic containers as follows:

NDC 0173-0412-00	1-g* Plastic Container (Carton of 24)
NDC 0173-0413-00	2-g* Plastic Container (Carton of 24)

*Equivalent to anhydrous ceftazidime.

REFERENCES

1. Bauer AW, Kirby WMM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized single disk method. *Am J Clin Pathol.* 1966;45:493–496.
2. National Committee for Clinical Laboratory Standards. *Approved Standard: Performance Standards for Antimicrobial Disc Susceptibility Tests.* (M2-A3). December 1984.
3. Certification procedure for antibiotic sensitivity discs (21 CFR 460.1). *Federal Register.* May 30, 1974;39:19182-19184.
4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31-41.

FORTAZ and ZINACEF are registered trademarks of Glaxo Wellcome.

ADD-Vantage is a registered trademark of Abbott Laboratories.

CLINITEST and CLINISTIX are registered trademarks of Ames Division, Miles Laboratories, Inc.

TES-TAPE is a registered trademark of Eli Lilly and Company.

GALAXY and VIAFLEX are registered trademarks of Baxter International Inc.

US Patents, 4,258,041; 4,329,453; and 4,582,830

February 1998/RL-545

Shown in Product Identification Guide, page 312 ℞

IMITREX®

[Im '-I-trĕx '] ℞

(sumatriptan succinate)
Injection

For Subcutaneous Use Only.

DESCRIPTION

IMITREX (sumatriptan succinate) Injection is a selective 5-hydroxytryptamine$_1$ receptor subtype agonist. Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulfonamide butane-1,4-dioate(1:1).

The empirical formula is $C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$, representing a molecular weight of 413.5.

Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline.

IMITREX Injection is a clear, colorless to pale yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 0.5 mL of solution contains 6 mg of sumatriptan (base) as the succinate salt and 3.5 mg of sodium chloride, USP in water for injection, USP. The pH range of the solution is approximately 4.2 to 5.3. The osmolality of the injection is 291 mOsmol.

CLINICAL PHARMACOLOGY

Mechanism of Action: Sumatriptan has been demonstrated to be a selective agonist for a vascular 5-hydroxytryptamine$_1$ receptor subtype (probably a member of the 5-HT$_{1D}$ family) with no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT$_2$, 5-HT$_3$ receptor subtypes or at alpha$_1$-, alpha$_2$-, or beta-adrenergic; dopamine$_1$; dopamine$_2$; muscarinic; or benzodiazepine receptors.

The vascular 5-HT$_1$ receptor subtype to which sumatriptan binds selectively, and through which it presumably exerts its antimigrainous effect, has been shown to be present on cranial arteries in both dog and primate, on the human basilar artery, and in the vasculature of the isolated dura mater of humans. In these tissues, sumatriptan activates this receptor to cause vasoconstriction, an action in humans correlating with the relief of migraine and cluster headache. In the anesthetized dog, sumatriptan selectively reduces the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. In the cat, sumatriptan selectively constricts the carotid arteriovenous anastomoses while having little effect on blood flow or resistance in cerebral or extracerebral tissues.

Corneal Opacities: Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg per day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established; however, the relative exposure at the lowest dose tested was approximately five times the human exposure after a 100-mg oral dose or three times the human exposure after a 6-mg subcutaneous dose.

Melanin Binding: In rats with a single subcutaneous dose (0.5 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 days, suggesting that sumatriptan and its metabolites bind to the melanin of the eye. The clinical significance of this binding is unknown.

Pharmacokinetics: Pharmacokinetic parameters following a 6-mg subcutaneous injection into the deltoid area of the arm in nine males (*mean age, 33 years; mean weight, 77 kg*) were systemic clearance: 1,194 ± 149 mL/min (*mean ± S.D.*), distribution half-life: 15 ± 2 minutes, terminal half-life: 115 ± 19 minutes, and volume of distribution central compartment: 50 ± 8 liters. Of this dose, 22% ± 4% was excreted in the urine as unchanged sumatriptan and 38% ± 7% as the indole acetic acid metabolite.

After a single 6-mg subcutaneous manual injection into the deltoid area of the arm in 18 healthy males (*age, 24 ± 6 years; weight, 70 kg*), the maximum serum concentration (C_{max}) was (*mean ± standard deviation*) 74 ± 15 ng/mL and the time to peak concentration (t_{max}) was 12 minutes after injection (*range, 5 to 20 minutes*). In this study, the same dose injected subcutaneously in the thigh gave a C_{max} of 61 ± 15 ng/mL by manual injection versus 52 ± 15 ng/mL by autoinjector techniques. The t_{max} or amount absorbed were not significantly altered by either the site or technique of injection.

The bioavailability of sumatriptan via subcutaneous site injection to 18 healthy male subjects was 97% ± 16% of that obtained following intravenous injection. Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL, is low, approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated.

Special Populations: ***Renal Impairment:*** The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined, but little clinical effect would be expected as sumatriptan is largely metabolized to an inactive substance.

Hepatic Impairment: The effect of hepatic disease on the pharmacokinetics of subcutaneously and orally administered sumatriptan has been evaluated. There were no statistically significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in hepatically impaired patients compared to healthy controls. However, the liver plays an important role in the presystemic clearance of orally administered sumatriptan. Accordingly, the bioavailability of sumatriptan following oral administration may be markedly increased in patients with liver disease. In one small study of hepatically impaired patients (n = 8) matched for sex, age, and weight with healthy subjects, the hepatically impaired patients had an approximately 70% increase in AUC and C_{max} and a t_{max} 40 minutes earlier compared to the healthy subjects.

Age: The pharmacokinetics of sumatriptan in the elderly (*mean age, 72 years; two males and four females*) and in

Continued on next page

This product information is based on labeling in effect on June 1, 1998. For further information, contact via direct mail, phone, or web site Medical Information: Glaxo Wellcome Inc., PO Box 13398, Research Triangle Park, NC 27709. Healthcare Professionals (Medical Information): 800-334-0089 Patients (Customer Response Center): 888-TALK2GW (1-888-825-5249) Glaxo Wellcome Corporate Web Site: www.glaxowellcome.com

...YCIN SULFATE

...® (Tobramycin Sulfate Injection, USP).

...CIN® HCl

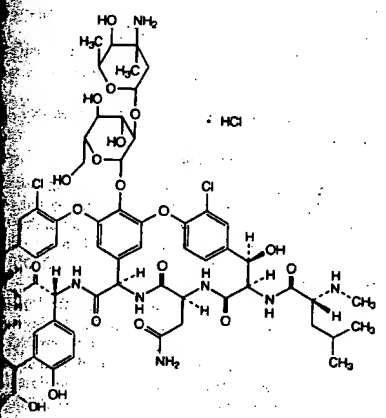
...in ăch 'sē-ĕl]

...ancomycin Hydrochloride, USP)

...TION

...HCl (Sterile Vancomycin Hydrochloride, USP), ... is a chromatographically purified, tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (*Nocardia orientalis*) and has the chemical formula $C_{66}H_{75}Cl_2N_9O_{24}$ • HCl. The molecular weight is 1,485.73; ... base is equivalent to 0.34 mmol.

... hydrochloride has the following structural



...ntain sterile vancomycin hydrochloride equiva... 500 mg or 1 g vancomycin activity. Vancomycin ...ride is an off-white lyophilized plug. When re... in water, it forms a clear solution with a pH ... to 4.5. This product is oxygen sensitive.

PHARMACOLOGY

... is poorly absorbed after oral administration; it ...venously for therapy of systemic infections. In... injection is painful.

...with normal kidney function, multiple intrave... of 1 g of vancomycin (15 mg/kg) infused over 60 ...uces mean plasma concentrations of approxi... µg/mL immediately after the completion of infu... plasma concentrations of approximately 23 ... after infusion, and mean plasma concentra... ximately 8 µg/mL 11 hours after the end of the ...ltiple dosing of 500 mg infused over 30 minutes ...an plasma concentrations of about 49 µg/mL at ...n of infusion, mean plasma concentrations of ...mL 2 hours after infusion, and mean plasma ... of about 10 µg/mL 6 hours after infusion. ...oncentrations during multiple dosing are sim... after a single dose.

...mination half-life of vancomycin from plasma ... in subjects with normal renal function. In the ... about 75% of an administered dose of vanco... ...ted in urine by glomerular filtration. Mean ...ance is about 0.058 L/kg/h, and mean renal ...about 0.048 L/kg/h. Renal dysfunction slows ex...ncomycin. In anephric patients, the average ...mination is 7.5 days. The distribution coeffi... 0.8 to 0.43 L/kg. There is no apparent metab... drug. About 60% of an intraperitoneal dose of ...dministered during peritoneal dialysis is ab...ically in 6 hours. Serum concentrations of ...L are achieved by intraperitoneal injection of ...ancomycin. Although vancomycin is not effec... by either hemodialysis or peritoneal dialysis, ...n reports of increased vancomycin clearance ...fusion and hemofiltration.

... and renal clearance of vancomycin may be ...elderly.

... approximately 55% serum protein bound as ...ultrafiltration at vancomycin serum concen... to 100 µg/mL. After IV administration of ...nhibitory concentrations are present in pleu..., ascitic, and synovial fluids; in urine; in peri... fluid; and in atrial appendage tissue. Vanco... not readily diffuse across normal meninges ...l fluid; but, when the meninges are inflamed, ...in the spinal fluid occurs.

The bactericidal action of vancomycin re... from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis. There is no cross-resistance between vancomycin and other antibiotics. Vancomycin is active against staphylococci, including *Staphylococcus aureus* and *Staphylococcus epidermidis* (including heterogeneous methicillin-resistant strains); streptococci, including *Streptococcus pyogenes, Streptococcus pneumoniae* (including penicillin-resistant strains), *Streptococcus agalactiae*, the viridans group, *Streptococcus bovis*, and enterococci (eg, *Enterococcus faecalis* [formerly *Streptococcus faecalis*]); *Clostridium difficile* (eg, toxigenic strains implicated in pseudomembranous enterocolitis); and diphtheroids. Other organisms that are susceptible to vancomycin in vitro include *Listeria monocytogenes, Lactobacillus* species, *Actinomyces* species, *Clostridium* species, and *Bacillus* species.

Vancomycin is not active in vitro against gram-negative bacilli, mycobacteria, or fungi.

Synergy —The combination of vancomycin and an aminoglycoside acts synergistically in vitro against many strains of *S. aureus*, nonenterococcal group D streptococci, enterococci, and *Streptococcus* species (viridans group).

Disk Susceptibility Tests —The standardized disk method described by the National Committee for Clinical Laboratory Standards has been recommended to test susceptibility to vancomycin. Results of standard susceptibility tests with a 30-µg vancomycin hydrochloride disk should be interpreted according to the following criteria: Susceptible organisms produce zones greater than or equal to 12 mm, indicating that the test organism is likely to respond to therapy. Organisms that produce zones of 10 or 11 mm are considered to be of intermediate susceptibility. Organisms in this category are likely to respond if the infection is confined to tissues or fluids in which high antibiotic concentrations are attained. Resistant organisms produce zones of 9 mm or less, indicating that other therapy should be selected.

Using a standardized dilution method, a bacterial isolate may be considered susceptible if the MIC value for vancomycin is 4 µg/mL or less. Organisms are considered resistant to vancomycin if the MIC is greater than or equal to 16 µg/mL. Organisms having an MIC value of less than 16 µg/mL but greater than 4 µg/mL are considered to be of intermediate susceptibility.[1-2]

Standardized procedures require the use of laboratory control organisms. The 30-µg vancomycin disk should give zone diameters between 15 and 19 mm for *S. aureus* ATCC 25923. As with the standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard vancomycin powder should give MIC values in the range of 0.5 µg/mL to 2.0 µg/mL for *S. aureus* ATCC 29213. For *E. faecalis* ATCC 29212, the MIC range should be 1.0 to 4.0 µg/mL.

INDICATIONS AND USAGE

Vancocin HCl is indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (beta-lactam-resistant) staphylococci. It is indicated for penicillin-allergic patients, for patients who cannot receive or who have failed to respond to other drugs, including the penicillins or cephalosporins, and for infections caused by vancomycin-susceptible organisms that are resistant to other antimicrobial drugs. Vancocin HCl is indicated for initial therapy when methicillin-resistant staphylococci are suspected, but after susceptibility data are available, therapy should be adjusted accordingly.

Vancocin HCl is effective in the treatment of staphylococcal endocarditis. Its effectiveness has been documented in other infections due to staphylococci, including septicemia, bone infections, lower respiratory tract infections, and skin and skin structure infections. When staphylococcal infections are localized and purulent, antibiotics are used as adjuncts to appropriate surgical measures.

Vancocin HCl has been reported to be effective alone or in combination with an aminoglycoside for endocarditis caused by *Streptococcus viridans* or *S. bovis*. For endocarditis caused by enterococci (eg, *E. faecalis*), Vancocin HCl has been reported to be effective only in combination with an aminoglycoside.

Vancocin HCl has been reported to be effective for the treatment of diphtheroid endocarditis. Vancocin HCl has been used successfully in combination with either rifampin, an aminoglycoside, or both in early-onset prosthetic valve endocarditis caused by *S. epidermidis* or diphtheroids.

Specimens for bacteriologic cultures should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to Vancocin HCl.

The parenteral form of Vancocin HCl may be administered orally for treatment of antibiotic-associated pseudomembranous colitis caused by *C. difficile* and for staphylococcal enterocolitis. Parenteral administration of Vancocin HCl alone is of unproven benefit for these indications. **Vancocin HCl is not effective by the oral route for other types of infection.** Although no controlled clinical efficacy studies have been conducted, intravenous vancomycin has been suggested by the American Heart Association and the American Dental Association as prophylaxis against bacterial endocarditis in penicillin-allergic patients who have congenital heart disease or rheumatic or other acquired valvular heart disease when these patients undergo dental procedures or surgical procedures of the upper respiratory tract.

Note: When selecting antibiotics for the prevention of bacterial endocarditis, the physician or dentist should read the full joint statement of the American Heart Association and the American Dental Association.[3]

CONTRAINDICATION

Vancocin HCl is contraindicated in patients with known hypersensitivity to this antibiotic.

WARNINGS

Rapid bolus administration (eg, over several minutes) may be associated with exaggerated hypotension, and, rarely, cardiac arrest.

Vancocin HCl should be administered in a dilute solution over a period of not less than 60 minutes to avoid rapid-infusion-related reactions. Stopping the infusion usually results in prompt cessation of these reactions.

Ototoxicity has occurred in patients receiving Vancocin HCl. It may be transient or permanent. It has been reported mostly in patients who have been given excessive doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Vancomycin should be used with caution in patients with renal insufficiency because the risk of toxicity is appreciably increased by high, prolonged blood concentrations.

Dosage of Vancocin HCl must be adjusted for patients with renal dysfunction (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION).

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including vancomycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis." After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

General —Clinically significant serum concentrations have been reported in some patients who have taken multiple oral doses of vancomycin for active *C. difficile*-induced pseudomembranous colitis.

Prolonged use of Vancocin HCl may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

In order to minimize the risk of nephrotoxicity when treating patients with underlying renal dysfunction or patients receiving concomitant therapy with an aminoglycoside, serial monitoring of renal function should be performed and particular care should be taken in following appropriate dosing schedules (*see* DOSAGE AND ADMINISTRATION).

Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.

Reversible neutropenia has been reported in patients receiving Vancocin HCl (*see* ADVERSE REACTIONS). Patients who will undergo prolonged therapy with Vancocin HCl or those who are receiving concomitant drugs that may cause neutropenia should have periodic monitoring of the leukocyte count.

Vancocin HCl is irritating to tissue and must be given by a secure intravenous route of administration. Pain, tenderness, and necrosis occur with intramuscular injection of Vancocin HCl or with inadvertent extravasation. Thrombophlebitis may occur, the frequency and severity of which can be minimized by administering the drug slowly as a dilute solution (2.5 to 5 g/L) and by rotating the sites of infusion. There have been reports that the frequency of infusion-related events (including hypotension, flushing, erythema, urticaria, and pruritus) increases with the concomitant administration of anesthetic agents. Infusion-related events may be minimized by the administration of Vancocin HCl as a 60-minute infusion prior to anesthetic induction.

Continued on next page

• **Identi-Code** symbol. This product information was prepared in June 1998. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5979.

Vancocin HCl Intravenous—Cont.

The safety and efficacy of vancomycin administration by the intrathecal (intralumbar or intraventricular) routes have not been assessed.

Reports have revealed that administration of sterile vancomycin HCl by the intraperitoneal route during continuous ambulatory peritoneal dialysis (CAPD) has resulted in a syndrome of chemical peritonitis. To date, this syndrome has ranged from a cloudy dialysate alone to a cloudy dialysate accompanied by variable degrees of abdominal pain and fever. This syndrome appears to be short-lived after discontinuation of intraperitoneal vancomycin.

Drug Interactions—Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing (*see* USAGE IN PEDIATRICS *under* PRECAUTIONS) and anaphylactoid reactions (*see* ADVERSE REACTIONS).

Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymyxin B, colistin, viomycin, or cisplatin, when indicated, requires careful monitoring.

Usage in Pregnancy—Pregnancy Category C—Animal reproduction studies have not been conducted with Vancocin HCl. It is not known whether Vancocin HCl can affect reproduction capacity. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of Vancocin HCl on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancocin HCl was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to Vancocin HCl was noted. One infant whose mother received Vancocin HCl in the third trimester experienced conductive hearing loss that was not attributed to the administration of Vancocin HCl. Because the number of patients treated in this study was limited and Vancocin HCl was administered only in the second and third trimesters, it is not known whether Vancocin HCl causes fetal harm. Vancocin HCl should be given to a pregnant woman only if clearly needed.

Nursing Mothers—Vancocin HCl is excreted in human milk. Caution should be exercised when Vancocin HCl is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Usage in Pediatrics—In premature neonates and young infants, it may be appropriate to confirm desired vancomycin serum concentrations. Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing in children (*see* ADVERSE REACTIONS).

Geriatrics—The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted. Vancomycin dosage schedules should be adjusted in elderly patients (*see* DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Infusion-Related Events—During or soon after rapid infusion of Vancocin HCl, patients may develop anaphylactoid reactions, including hypotension (*see* ANIMAL PHARMACOLOGY), wheezing, dyspnea, urticaria, or pruritus. Rapid infusion may also cause flushing of the upper body ("Red Man Syndrome") or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours. Such events are infrequent if Vancocin HCl is given by a slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when Vancocin HCl was administered at a rate of 10 mg/min or less.

Nephrotoxicity—Rarely, renal failure, principally manifested by increased serum creatinine or BUN concentrations, especially in patients given large doses of Vancocin HCl, has been reported. Rare cases of interstitial nephritis have been reported. Most of these have occurred in patients who were given aminoglycosides concomitantly or who had preexisting kidney dysfunction. When Vancocin HCl was discontinued, azotemia resolved in most patients.

Gastrointestinal—Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (*see* WARNINGS).

Ototoxicity—A few dozen cases of hearing loss associated with Vancocin HCl have been reported. Most of these patients had kidney dysfunction or a preexisting hearing loss or were receiving concomitant treatment with an ototoxic drug. Vertigo, dizziness, and tinnitus have been reported rarely.

Hematopoietic—Reversible neutropenia, usually starting 1 week or more after onset of therapy with Vancocin HCl or after a total dosage of more than 25 g, has been reported for several dozen patients. Neutropenia appears to be promptly reversible when Vancocin HCl is discontinued. Thrombocytopenia has rarely been reported.

Although a causal relationship has not been established, reversible agranulocytosis (granulocytes <500/mm^3) has been reported rarely.

Phlebitis—Inflammation at the injection site has been reported.

Miscellaneous—Infrequently, patients have been reported to have had anaphylaxis, drug fever, nausea, chills, eosinophilia, rashes (including exfoliative dermatitis), Stevens-Johnson syndrome, toxic epidermal necrolysis, and rare cases of vasculitis in association with administration of Vancocin HCl.

Chemical peritonitis has been reported following intraperitoneal administration of vancomycin (*see* PRECAUTIONS).

OVERDOSAGE

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Hemofiltration and hemoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance. The median lethal intravenous dose is 319 mg/kg in rats and 400 mg/kg in mice.

To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

DOSAGE AND ADMINISTRATION

Infusion-related events are related to both concentration and rate of administration of vancomycin. Concentrations of no more than 5 mg/mL and rates of no more than 10 mg/min are recommended in adults (see also age-specific recommendations). In selected patients in need of fluid restriction, a concentration up to 10 mg/mL may be used; use of such higher concentrations may increase the risk of infusion-related events. Infusion-related events may occur, however, at any rate or concentration.

Patients With Normal Renal Function

Adults—The usual daily intravenous dose is 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours. Each dose should be administered at no more than 10 mg/min or over a period of at least 60 minutes, whichever is longer. Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose.

Children—The usual intravenous dosage of Vancocin HCl is 10 mg/kg per dose given every 6 hours. Each dose should be administered over a period of at least 60 minutes.

Infants and Neonates—In neonates and young infants, the total daily intravenous dosage may be lower. In both neonates and infants, an initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the 1st week of life and every 8 hours thereafter up to the age of 1 month. Each dose should be administered over 60 minutes. Close monitoring of serum concentrations of vancomycin may be warranted in these patients.

Patients With Impaired Renal Function and Elderly Patients

Dosage adjustment must be made in patients with impaired renal function. In premature infants and the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Measurement of vancomycin serum concentrations can be helpful in optimizing therapy, especially in seriously ill patients with changing renal function. Vancomycin serum concentrations can be determined by use of microbiologic assay, radioimmunoassay, fluorescence polarization immunoassay, fluorescence immunoassay, or high-pressure liquid chromatography.

If creatinine clearance can be measured or estimated accurately, the dosage for most patients with renal impairment can be calculated using the following table. The dosage of Vancocin HCl per day in mg is about 15 times the glomerular filtration rate in mL/min.

DOSAGE TABLE FOR VANCOMYCIN IN PATIENTS WITH IMPAIRED RENAL FUNCTION
(Adapted from Moellering et al)*

Creatinine Clearance mL/min	Vancomycin Dose mg/24 h
100	1,545
90	1,390
80	1,235
70	1,080
60	925
50	770
40	620
30	465
20	310
10	155

The initial dose should be no less than 15 mg/kg, even in patients with mild to moderate renal insufficiency.

The table is not valid for functionally anephric patients. For such patients, an initial dose of 15 mg/kg of body weight should be given to achieve prompt therapeutic serum concentrations. The dose required to maintain stable concentrations is 1.9 mg/kg/24 h. In patients with mod... inpairment, it may be more convenient to give ma... doses of 250 to 1,000 mg once every several days ... administering the drug on a daily basis. In anuri... 1,000 mg every 7 to 10 days has been recommend... When only the serum creatinine concentration ... the following formula (based on sex, weight, and ... patient) may be used to calculate creatinine ... culated creatinine clearances (mL/min) are only ... The creatinine clearance should be measured pr...

Men: $\frac{\text{Weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine concentration}}$

Women: 0.85 × above value

The serum creatinine must represent a steady ... function. Otherwise, the estimated value for ... clearance is not valid. Such a calculated clear... overestimate of actual clearance in patients with ... (1) characterized by decreasing renal functio... shock, severe heart failure, or oliguria; (2) in w... mal relationship between muscle mass and ... weight is not present, such as obese patients or ... liver disease, edema, or ascites; and (3) accompa... bilitation, malnutrition, or inactivity.

The safety and efficacy of vancomycin administ... intrathecal (intralumbar or intraventricular) ... not been assessed.

Intermittent infusion is the recommended ... administration.

PREPARATION AND STABILITY

At the time of use, reconstitute by adding ... Sterile Water for Injection to the 500-mg vial or ... Sterile Water for Injection to the 1-g vial of dry ... comycin powder. Vials reconstituted in this ... give a solution of 50 mg/mL. FURTHER DI... REQUIRED.

After reconstitution with Sterile Water for In... als may be stored in a refrigerator for 14 days ... nificant loss of potency. Reconstituted solutions ... 500 mg of vancomycin must be diluted with at ... of diluent. Reconstituted solutions containing ... vancomycin must be diluted with at least 100 mL ... Reconstituted solutions containing 1 g of vanco... be diluted with at least 200 mL of diluent. The ... diluted in this manner, should be administered ... tent intravenous infusion over a period of ... minutes.

Compatibility With Intravenous Fluids—Solutions ... diluted with 5% Dextrose Injection or 0.9% Sodium ... Injection may be stored in a refrigerator for 14 days ... significant loss of potency. Solutions that are ... the following infusion fluids may be stored in a ... for 96 hours:

5% Dextrose Injection and 0.9% Sodium Chlo... tion, USP
Lactated Ringer's Injection, USP
Lactated Ringer's and 5% Dextrose Injection
Normosol®-M* and 5% Dextrose
Isolyte® E**
Acetated Ringer's Injection

Vancomycin solution has a low pH and may ... or physical instability when it is mixed ... compounds.

Prior to administration, parenteral drug prod... inspected visually for particulate matter and ... whenever solution or container permits.

For Oral Administration—Oral Vancocin HCl ... treating antibiotic-associated pseudomembra... caused by *C. difficile* and for staphylococcal ... Vancocin HCl is not effective by the oral ... types of infections. The usual adult total daily ... mg to 2 g given in 3 or 4 divided doses for 7 to ... total daily dosage in children is 40 mg/kg of ... 3 or 4 divided doses for 7 to 10 days. The total ... should not exceed 2 g. The appropriate dose ... in 1 oz of water and given to the patient to ... flavoring syrups may be added to the solution ... the taste for oral administration. The diluted ... be administered via a nasogastric tube.

*Normosol®-M, Abbott Hospital Products (Division of Abbott Laboratories)

**Isolyte® E, McGaw, Inc.

HOW SUPPLIED

Vancocin® HCl Vials (or Sterile Vancomycin ... USP) are available in:

The 500 mg,* 10-mL vials are available as ...
10-mL vials NDC 0002-1444-01 (VL ...
Traypak† of 25 NDC 0002-1444-25 (VL ...

The 1 g,* 20-mL vials are available as follows:
Traypak of 25 NDC 0002-7321-25 (VL ...

Also available:

Vancocin-HCl ADD-Vantage‡ Vials (or Ster... Hydrochloride, USP) are available in:

The 500 mg,* 15-mL vials are available as ...
Traypak of 10 NDC 0002-7297-10 (VL ...

...1 g,* 15-mL vials are available as follows:
...Traypak of 10 NDC 0002-7298-10 (VL 7298)
...Vancocin HCl Pharmacy Bulk Package (or Vancomycin Hydrochloride for Injection, USP) are available in:
...10 g,* 100-mL vials are available as follows:
...100-mL vial NDC 0002-7355-01 (VL 7355)
...Prior to reconstitution, the vials may be stored at room temperature, 59° to 86°F (15° to 30°C).

...equivalent to vancomycin.
...Traypak™ (multivial carton, Lilly).
...ADD-Vantage® (vials and diluent containers, Abbott).
...CAUTION—Federal (USA) law prohibits dispensing without prescription.

...IMAL PHARMACOLOGY

...animal studies, hypotension and bradycardia occurred in ... receiving an intravenous infusion of vancomycin hydrochloride, 25 mg/kg, at a concentration of 25 mg/mL and ... infusion rate of 13.3 mL/min.

...ERENCES

...ational Committee for Clinical Laboratory Standards. ...erformance Standards for Antimicrobial Disk Susceptibility Tests–Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.

...ational Committee for Clinical Laboratory Standards. ...ethods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically–Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.

...al, Adnan S, et al: Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *JAMA* 264 (22):2919–2922, December 12, 1990.

...ehering RC, Krogstad DJ, Greenblatt DJ: Vancomycin therapy in patients with impaired renal function: A nomogram for dosage. *Ann Intern Med* 1981;94:343.

...ure revised June 13, 1997.

...AMP [061397]

...COCIN HCl Rx

...ə-sin ăch 'sē-ĕl }
...ycin hydrochloride)
...al Solution, USP

...peration for the treatment of colitis is for oral use ... is not systemically absorbed. Vancocin® HCl must ... orally for treatment of staphylococcal enterocolitis ... antibiotic-associated pseudomembranous colitis ... by *Clostridium difficile*. Orally administered Vancocin ... not effective for other types of infection.

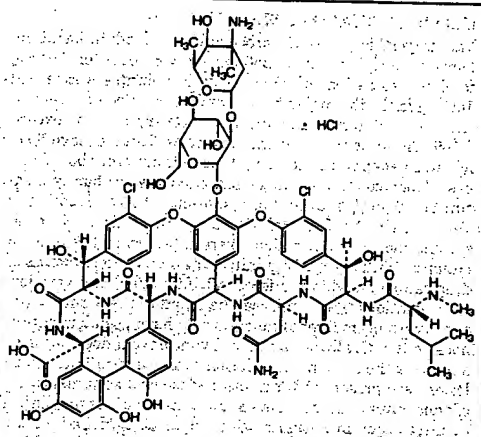
... administration of Vancocin HCl is not effective ... treatment of staphylococcal enterocolitis and ... associated pseudomembranous colitis caused by ... If parenteral vancomycin therapy is desired, use ... HCl (Sterile Vancomycin Hydrochloride, USP), ..., and consult package insert accompanying ... preparation.

...TION

... HCl for Oral Solution (Vancomycin Hydrochloride ... Solution, USP), contains chromatographically ...ancomycin hydrochloride, a tricyclic glycopeptide ...ived from *Amycolatopsis orientalis* (formerly ... *orientalis*), which has the chemical formula ...$_{66}$H$_{75}$Cl$_2$N$_9$O$_{24}$ • HCl. The molecular weight of vancomycin ... is 1,485.73; 500 mg of the base is equivalent ...

... HCl for Oral Solution contains vancomycin hydro... equivalent to 10 g (6.7 mmol) or 1 g (0.67 mmol) ... Calcium disodium edetate, equivalent to 0.2 ... per gram of vancomycin, is added at the time of ... The 10-g bottle may contain up to 40 mg of ... gram of vancomycin.

...ydrochloride has the following structure:



...[structure at top of next column]

...PHARMACOLOGY

... poorly absorbed after oral administration. ...e dosing of 250 mg every 8 hours for 7 doses, ...rations of vancomycin in volunteers exceeded ... the majority of samples. No blood concentrations ...ected and urinary recovery did not exceed ...bric patients with no inflammatory bowel ... concentrations of vancomycin were barely ...0.66 µg/mL) in 2 of 5 subjects who received 2 g ... for Oral Solution daily for 16 days. No measurable concentrations were attained in the other 3 ... doses of 2 g daily, very high concentrations of ... found in the feces (>3,100 mg/kg) and very low ...(<1 µg/mL) can be found in the serum of patients with normal renal function who have pseudomembranous colitis. Orally administered vancomycin does not usually enter systemic circulation even when inflammatory ...ment. After multiple-dose oral administration of vancomycin, measurable serum concentrations may infrequently occur in patients with active *C. difficile*-induced pseudomembranous colitis, and, in the presence of renal impairment, the possibility of accumulation exists.

Microbiology —The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis. There is no cross-resistance between vancomycin and other antibiotics. Vancomycin is active against *C. difficile* (eg, toxigenic strains implicated in pseudomembranous enterocolitis). It is also active against staphylococci, including *Staphylococcus aureus*.

For further information, see prescribing information for Vancocin HCl, IntraVenous.

Vancomycin is not active in vitro against gram-negative bacilli, mycobacteria, or fungi.

Disk Susceptibility Tests —The standardized disk and/or dilution methods described by the National Committee for Clinical Laboratory Standards have been recommended to test susceptibility to vancomycin.

INDICATIONS AND USAGE

Vancocin HCl for Oral Solution is administered orally for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *C. difficile*. Parenteral administration of Vancocin HCl is not effective for the above indications; therefore, Vancocin HCl must be given orally for these indications. **Orally administered Vancocin HCl is not effective for other types of infection.**

CONTRAINDICATION

Vancocin HCl is contraindicated in patients with known hypersensitivity to this antibiotic.

PRECAUTIONS

General —Clinically significant serum concentrations have been reported in some patients who have taken multiple oral doses of vancomycin for active *C. difficile*-induced pseudomembranous colitis; therefore, monitoring of serum concentrations may be appropriate.

Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of vancomycin and, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of vancomycin (See package insert accompanying the intravenous preparation.) The risk is greater if renal impairment is present. It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly.

Ototoxicity has occurred in patients receiving Vancocin HCl. It may be transient or permanent. It has been reported mostly in patients who have been given excessive intravenous doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.

When patients with underlying renal dysfunction or those receiving concomitant therapy with an aminoglycoside are being treated, serial monitoring of renal function should be performed.

Usage in Pregnancy —Pregnancy Category C —Animal reproduction studies have not been conducted with Vancocin HCl. It is not known whether Vancocin HCl can affect reproduction capacity. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of Vancocin HCl on infants were evaluated when the drug was administered intravenously to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancocin HCl was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to Vancocin HCl was noted. One infant whose mother received Vancocin HCl in the third trimester experienced conductive hearing loss that was not attributed to the administration of Vancocin HCl. Because the number of patients treated in this study was limited and Vancocin HCl was administered only in the second and third trimesters, it is not known whether Vancocin HCl causes fetal harm. Vancocin HCl should be given to a pregnant woman only if clearly needed.

Nursing Mothers —Vancocin HCl is excreted in human milk based on information obtained with the intravenous administration of Vancocin HCl. Blood concentrations achieved with oral administration are very low. (*see* CLINICAL PHARMACOLOGY). Caution should be exercised when Vancocin HCl is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

Nephrotoxicity —Rarely, renal failure, principally manifested by increased serum creatinine or BUN concentrations, especially in patients given large doses of intravenously administered Vancocin HCl, has been reported. Rare cases of interstitial nephritis have been reported. Most of these have occurred in patients who were given aminoglycosides concomitantly or who had preexisting kidney dysfunction. When Vancocin HCl was discontinued, azotemia resolved in most patients.

Ototoxicity —A few dozen cases of hearing loss associated with intravenously administered Vancocin HCl have been reported. Most of these patients had kidney dysfunction or a preexisting hearing loss or were receiving concomitant treatment with an ototoxic drug. Vertigo, dizziness, and tinnitus have been reported rarely.

Hematopoietic —Reversible neutropenia, usually starting 1 week or more after onset of intravenous therapy with Vancocin HCl or after a total dosage of more than 25 g, has been reported for several dozen patients. Neutropenia appears to be promptly reversible when Vancocin HCl is discontinued. Thrombocytopenia has rarely been reported.

Miscellaneous —Infrequently, patients have been reported to have had anaphylaxis, drug fever, chills, nausea, eosinophilia, rashes (including exfoliative dermatitis), Stevens-Johnson syndrome, toxic epidermal necrolysis, and rare cases of vasculitis in association with the administration of Vancocin HCl.

A condition has been reported that is similar to the IV-induced syndrome with symptoms consistent with anaphylactoid reactions, including hypotension, wheezing, dyspnea, urticaria, pruritus, flushing of the upper body ("Red Man Syndrome"), pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours.

OVERDOSAGE

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Hemofiltration and hemoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance.

Treatment —To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

DOSAGE AND ADMINISTRATION

Adults —Oral Vancocin HCl is used in treating antibiotic-associated pseudomembranous colitis caused by *C. difficile* and staphylococcal enterocolitis. Vancocin HCl is not effective by the oral route for other types of infections. The usual adult total daily dosage is 500 mg to 2 g administered orally in 3 or 4 divided doses for 7 to 10 days.

Pediatric Patients —The usual daily dosage is 40 mg/kg in 3 or 4 divided doses for 7 to 10 days. The total daily dosage should not exceed 2 g.

PREPARATION AND STABILITY

The contents of the 10-g bottle may be mixed with distilled or deionized water (115 mL) for oral administration. When mixed with 115 mL of water, each 6 mL provides approximately 500 mg of vancomycin. The contents of the 1-g bottle may be mixed with distilled or deionized water (20 mL). When reconstituted with 20 mL, each 5 mL contains approximately 250 mg of vancomycin. Mix thoroughly to dissolve. These mixtures may be kept for 2 weeks in a refrigerator without significant loss of potency.

The appropriate oral solution dose may be diluted in 1 oz of water and given to the patient to drink. Common flavoring syrups may be added to the solution to improve the taste for

Continued on next page

---

* Identi-Code® symbol. This product information was prepared in June 1998. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5979.

Appendix B:

Pages 183 and 1939 of *Stedman's Medical Dictionary*, 26th Edition, 1995

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

STEDMAN'S Medical Dictionary

26th Edition

ILLUSTRATED IN

STEDMAN'S
Medical Dictionary

26th Edition

ILLUSTRATED IN **COLOR**

Editor: Marjory Spraycar
Senior Editor: Elizabeth Randolph
Editorial Assistant: Maureen Barlow Pugh
Copy Editors: Christopher Muldor, Jane Sellman, Barbara Werner
On-Line Editors: Kathryn J. Cadle, Barbara L. Ferretti, Catherine N. Kelly, Leslie Simpson
Editorial Proofreaders: Peter W. Binns, Jolanta Obrebska, Carol Sorgen
Medical Proofreaders: Alfred Jay Bollet, M.D.; John H. Dirckx, M.D.; Thomas W. Filardo, M.D.; Robert Hogan, M.D.; Edward Stim, M.D.
Database Programmers: Dennis P. Smithers, Dave Marcus, Lexi-Comp Inc., Hudson, OH
Production Coordinator: Paula K. Huber
Printing Coordinator: Brian Smith
Illustration Planning: Wayne J. Hubbel
Design: Robert C. Och, Dan Pfisterer
Cover Design: Sharon Reuter, Reuter & Associates

Database design by Lexi-Comp Inc., Hudson, OH
Printed in the United States of America by R.R. Donnelley & Sons Company

English Language Co-editions
Asian 1967, 1972, 1976
Indian 1967, 1973
Taiwan 1972, 1978

Translated Editions
Greek 1976
Indian 1977
Japanese 1977, 1985, 1995
Portuguese 1976, 1995
Spanish 1993

Library of Congress Cataloging-in-Publication Data

Stedman, Thomas Lathrop, 1853-1938.
[Medical dictionary]
Stedman's medical dictionary.—26th ed.
p. cm.
ISBN 0-683-07922-0 REGULAR EDITION
ISBN 0-683-07935-2 DELUXE EDITION
1. Medicine—Dictionaries. I. Title. II. Title: Medical dictionary.
[DNLM: 1. Dictionaries, Medical. W 13 S812m 1995]
R121.58 1995
610'.3—dc20
DNLM/DLC
for Library of Congress

quence, *B.* is no longer used in bacteriology. Identifiable organisms formerly placed in the genus *B.* have all been transferred to other genera. Specifically, *B. anitratum* is now known as *Acinetobacter calcoaceticus; B. coli* is now called *Escherichia coli.* [Mod. L. fr. G. *baktērion,* dim. of *baktron,* a staff or club]

bac·te·ri·um, pl. **bac·te·ria** (bak-tēr'ē-ŭm, -ă). A unicellular prokaryotic microorganism that usually multiplies by cell division and has a cell wall that provides a constancy of form; they may be aerobic or anaerobic, motile or nonmotile, and free-living, saprophytic, parasitic, or pathogenic. SEE ALSO Cyanobacteria. [Mod. L. fr. G. *baktērion,* dim. of *baktron,* a staff]

Blinn's b., a type of the typhoid-paratyphoid subgroups of the nonlactose-fermenting bacteria.

blue-green b., SEE Cyanobacteria.

Chauveau's b., former name for *Clostridium chauvoei.*

endoteric b., a b. that forms an endotoxin.

exoteric b., a b. that secretes an exotoxin.

lysogenic b., (1) a b. in the symbiotic condition in which its genome includes the genome (probacteriophage) of a temperate bacteriophage; in occasional instances the probacteriophage dissociates from the bacterial genome, develops into vegetative bacteriophage, and then matures, causing lysis of the respective host b. and release into the culture medium of infective temperate bacteriophage; (2) formerly, a pseudolysogenic bacterial strain, *i.e.,* a "carrier" strain of bacteriophage of low infectivity.

pyogenic b., a b. that causes a pyogenic infection, such as the pyogenic cocci (staphylococci, streptococci, pneumococci, meningococci) and *Haemophilus influenzae.*

bac·te·ri·u·ria (bak-tēr-ē-ū'rē-ă). The presence of bacteria in the urine.

bac·te·roid (bak'ter-oyd). Resembling bacteria.

Bac·te·roi·da·ce·ae (bak'ter-oy-dā'sē-ē). A family of obligate anaerobic (microaerophilic species may occur), nonsporeforming bacteria (order Eubacteriales) containing Gram-negative rods which vary in size from minute, filterable forms to long, filamentous, branching forms; pronounced pleomorphism may occur. Motile and nonmotile species occur; motile cells are peritrichous. Body fluids are frequently required for growth. Carbohydrates are usually fermented with the production of acid; gas may be produced in glucose or peptone media. These organisms occur primarily in the intestinal tracts and mucous membranes of warm-blooded animals. They may be pathogenic. The type genus is *Bacteroides.*

Bac·te·roi·des (bak-ter-oy'dēz). A genus of obligate anaerobic, nonsporeforming bacteria (family Bacteroidaceae) containing Gram-negative rods. Both motile and nonmotile species occur; motile cells are peritrichous. Some species ferment carbohydrates and produce combinations of succinic, lactic, acetic, formic, or propionic acids, sometimes with short-chained alcohols; butyric acid is not a major product. Those species which do not ferment carbohydrates produce from peptone either trace to moderate amounts of succinic, formic, acetic, and lactic acids or major amounts of acetic and butyric acids with moderate amounts of alcohols and isovaleric, propionic, and isobutyric acids. They are part of the normal flora of the oral, respiratory, intestinal, and urogenital cavities of humans and animals; some species are pathogenic. The type species is *B. fragilis.* [G. *bacterion* + *eidos,* form]

B. bivius, a species usually isolated from urogenital and abdominal infections and linked to pelvic inflammatory disease.

B. capillo'sus, a species isolated from human cysts and wounds, the mouth, and feces, and from the intestinal tracts of some animals.

B. corro'dens, former name for *Eikenella corrodens.*

B. di'siens, a species isolated from abdominal and urogenital infections, and from the mouth. SYN *Prevotella disiens.*

B. frag'ilis, a species that is one of the predominant organisms in the lower intestinal tract of man and other animals; also found in specimens from appendicitis, peritonitis, rectal abscesses, pilonidal cysts, surgical wounds, and lesions of the urogenital tract; it is the type species of the genus *B.*

B. furco'sus, a species found in an infected appendix, in lung and abdominal abscesses, and in feces.

B. melaninogenicus, SYN *Prevotella melaninogenica.*

B. nodo'sus, a species involved in the causation of foot rot in sheep and goats. SYN *Dichelobacter nodosus.*

B. ora'lis, a species found in the gingival crevice area of man and in infections of the oral cavity and upper respiratory and genital tracts. SYN *Prevotella oralis.*

B. o'ris, a species isloated from the gingival crevice, systemic infections, face, neck, and chest abscesses, wound drainages, and blood and various bodily fluids. SYN *Prevotella oris.*

B. pneumosin'tes, a species found in the nasopharynx, gingival crevice and periodontal pockets, blood, respiratory tract, brain abscesses, and head and neck infections.

B. praeacu'tus, a species isolated from the intestinal tracts of infants and adults, gangrenous lesions, lung abscesses, and blood. SYN *Tissierella praeacuta.*

B. putredi'nis, a species isolated from feces, cases of acute appendicitis, and abdominal and rectal abscesses; also from foot rot of sheep and from farm soil.

B. thetaiotamicron, a species implicated in intra-abdominal infections.

B. ureolyt'icus, a species isolated from infections of the respiratory and intestinal tracts, and from the buccal cavity, intestinal tract, urogenital tract, and blood after a dental extraction.

bac·te·roi·do·sis (bak'ter-oy-dō'sis). Rarely used term for an infection with *Bacteroides.*

bac·u·li·form (bă-kyū'li-fōrm). Rod-shaped. [L. *baculum,* a rod, + *forma,* form]

Bac·u·lo·vi·ri·dae (bak-yū-lō-vir'i-dē). A family of viruses that multiply only in invertebrates; virions are rod-shaped and measure 40 to 70 nm by 250 to 400 nm; genomes are of double-stranded, supercoiled DNA (MW 80 to 100 × 10^6). Genera of viruses that multiply only in invertebrates are also included in other families: *Iridovirus* (Iridoviridae), *Entomopoxvirus* (Poxviridae), *Densovirus* (Parvoviridae), cytoplasmic polyhedral virus group (Reoviridae), and *Sigmavirus* (Rhabdoviridae). Baculovirus derived vectors are frequently used to express foreign genes in insect cells. [L. *baculum,* rod]

bac·u·lo·vi·rus (bak'ū-lō-vī-rŭs). A virus that infects insect cells; used extensively in expression systems for recombinant proteins that require eucaryotic processing systems. [L. *baculum,* rod, + virus]

bac·u·lum (bak'yū-lŭm). SYN *os* penis. [L. a rod]

Baehr, George, U.S. physician, 1887–1978. SEE B.-Lohlein *lesion.*

Baelz, Erwin, German physician in Tokyo, 1849–1913. SEE B.'s *disease.*

BAER Abbreviation for brainstem auditory evoked response. SEE evoked *response.*

Baer, Karl E. von, German-Russian embryologist, 1792–1876. SEE B.'s *law, vesicle.*

Baer's ves·i·cle. See under vesicle.

Baeyer, Johann F.W.A. von, German chemist and Nobel laureate, 1835–1917. SEE B.'s *theory.*

bag. A pouch, sac, or receptacle. [A.S. *baelg*]

Ambu b., proprietary name for a self-reinflating b. with nonrebreathing valves to provide positive pressure ventilation during resuscitation with oxygen or air.

breathing b., a collapsible reservoir from which gases are inhaled and into which gases may be exhaled during general anesthesia or artificial ventilation. SYN reservoir b.

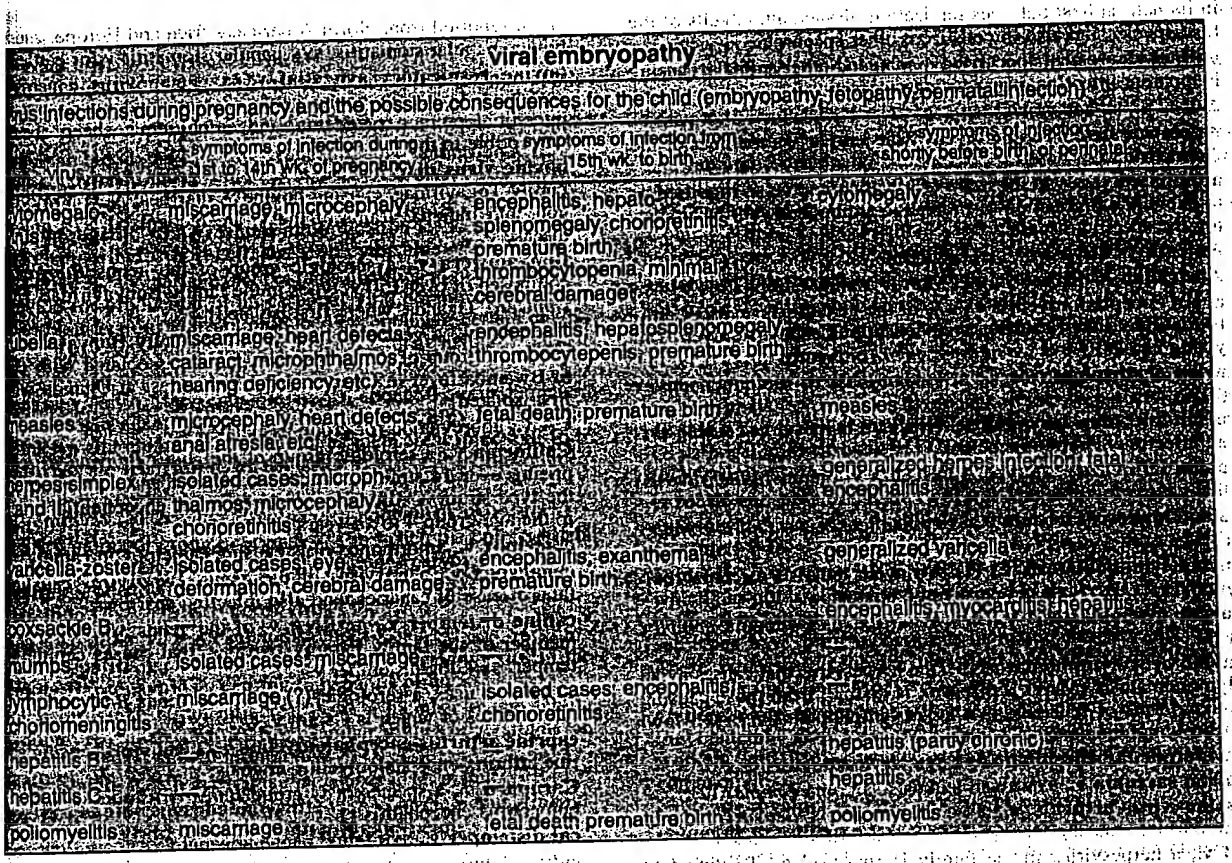
colostomy b., a bag worn over an artifical anus to collect feces.

Douglas b., a large b. in which expired gas is collected for several minutes to determine oxygen consumption in humans under conditions of actual work. [C.G. Douglas]

nuclear b., the aggregation of nuclei occurring in the nonstriated center of an intrafusal muscle fiber of a neuromuscular spindle.

Petersen's b., an obsolete device consisting of a rubber b. introduced into the rectum and inflated to push up the bladder to facilitate suprapubic cystotomy.

Politzer b., a pear-shaped rubber b. used for forcing air through the eustachian tube by the Politzer method.



than a virus (MW 75,000-100,000) and differs from one in that it consists only of single-stranded closed circular RNA, lacking a protein covering (capsid); replication does not depend on a helper virus, but is mediated by host cell enzymes. [virus + G. *eidos*, resemblance]

vi·r·l·gist (vī-rol′ō-jist). A specialist in virology.

vi·r·l·o·gy (vī-rol′ō-jē, vi-). The study of viruses and of virus disease. [virus + G. *logos*, study]

vi·ro·pex·is (vī-rō-pek′sis). Binding of virus to a cell and subsequent absorption (engulfment) of virus particles by that cell. [viro- + G. *pēxis*, fixation]

vi·ru·ci·dal (vī-rū-sī′dăl). Destructive to a virus. SYN viricidal.

vi·ru·cide (vī-rū-sīd). An agent active against virus infections. SYN viricide. [virus + L. *caedo*, to kill]

vi·ru·c·pria (vī-rū-kō′prē-ă). Presence of virus in feces. [virus + G. *kopros*, feces]

vir·u·lence. The disease-evoking power of a pathogen; numerically expressed as the ratio of the number of cases of overt infection to the total number infected, as determined by immunoassay. [L. *virulentia*, fr. *virulentus*, poisonous]

vir·u·lent (vir′ū-lent). Extremely toxic, denoting a markedly pathogenic microorganism. [L. *virulentus*, poisonous]

vir·u·lif·er·ous (vī-rū-lif′er-ŭs). Conveying virus.

vir·u·ria (vī-rū′rē-ă). Presence of viruses in the urine. [virus + G. *ouron*, urine]

VIRUS

vi·rus, pl. **vi·rus·es** (vī′rŭs). **1.** Formerly, the specific agent of an infectious disease. **2.** Specifically, a term for a group of infectious agents which, with few exceptions, are capable of passing through fine filters that retain most bacteria, are usually not visible through the light microscope, lack independent metabolism, and are incapable of growth or reproduction apart from living cells. They have a prokaryotic genetic apparatus but differ sharply from bacteria in other respects. The complete particle usually contains only DNA or RNA, not both, and is usually covered by a protein shell or capsid that protects the nucleic acid. They range in size from 15 mm up to several hundred mm. Classification of v.'s depends upon characteristics of virions as well as upon mode of transmission, host range, symptomatology, and other factors. For v.'s not listed below, see the specific name. SYN filtrable v., ultravirus. **3.** Relating to or caused by a v., as a virus disease. [L. poison]

2060 v., a strain of common cold v.; early isolate of *Rhinovirus*. SYN JH v.

Abelson murine leukemia v., a retrovirus belonging to the Type C retrovirus group subfamily (family Oncovirinae) which is associated with leukemia and produces *in vitro* transformation of mouse cells.

adeno-associated v. (AAV), SYN *Dependovirus*.

adenoidal-pharyngeal-conjunctival v., SYN adenovirus.

adenosatellite v., SYN *Dependovirus*.

African horse sickness v., a v. of the genus *Orbivirus*, in the family Reoviridae; the cause of African horse sickness.

African swine fever v., a DNA v. related to the family Iridoviridae and the etiologic agent of African swine fever.

AIDS-related v. (ARV), obsolete term for human immunodeficiency v.

Akabane v., a v. of the genus *Bunyavirus*, family Bunyaviridae, causing abortion in cattle and congenital arthrogryposis and hydranencephaly in bovine fetuses in Israel, Japan, and Australia; it is transmitted by mosquitoes.

Aleutian mink disease v., a v. of the genus *Parvovirus* causing Aleutian mink disease.

amphotropic v., an oncornavirus that does not produce disease

Appendix C:

"The Rise of Antibiotic-Resistant Infections," by
Ricki Lewis, Ph.D.,
FDA Consumer Magazine (Sept. 1995), at
http://www.fda.gov/fdac/features/795_antibio.html

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

U.S. Food and Drug Administration

The Rise of Antibiotic-Resistant Infections

by Ricki Lewis, Ph.D.

When penicillin became widely available during the second world war, it was a medical miracle, rapidly vanquishing the biggest wartime killer--infected wounds. Discovered initially by a French medical student, Ernest Duchesne, in 1896, and then rediscovered by Scottish physician Alexander Fleming in 1928, the product of the soil mold Penicillium crippled many types of disease-causing bacteria. But just four years after drug companies began mass-producing penicillin in 1943, microbes began appearing that could resist it.

The first bug to battle penicillin was Staphylococcus aureus. This bacterium is often a harmless passenger in the human body, but it can cause illness, such as pneumonia or toxic shock syndrome, when it overgrows or produces a toxin.

In 1967, another type of penicillin-resistant pneumonia, caused by Streptococcus pneumoniae and called pneumococcus, surfaced in a remote village in Papua New Guinea. At about the same time, American military personnel in southeast Asia were acquiring penicillin-resistant gonorrhea from prostitutes. By 1976, when the soldiers had come home, they brought the new strain of gonorrhea with them, and physicians had to find new drugs to treat it. In 1983, a hospital-acquired intestinal infection caused by the bacterium Enterococcus faecium joined the list of bugs that outwit penicillin.

Antibiotic resistance spreads fast. Between 1979 and 1987, for example, only 0.02 percent of pneumococcus strains infecting a large number of patients surveyed by the national Centers for Disease Control and Prevention were penicillin-resistant. CDC's survey included 13 hospitals in 12 states. Today, 6.6 percent of pneumococcus strains are resistant, according to a report in the June 15, 1994, Journal of the American Medical Association by Robert F. Breiman, M.D., and colleagues at CDC. The agency also reports that in 1992, 13,300 hospital patients died of bacterial infections that were resistant to antibiotic treatment.

Why has this happened?

"There was complacency in the 1980s. The perception was that we had licked the bacterial infection problem. Drug companies weren't working on new agents. They were concentrating on other areas, such as viral infections," says Michael Blum, M.D., medical officer in the Food and Drug Administration's division of anti-infective drug products. "In the meantime, resistance increased to a number of commonly used antibiotics, possibly related to overuse of antibiotics. In the 1990s, we've come to a point for certain infections that we don't have agents available."

According to a report in the April 28, 1994, New England Journal of Medicine, researchers have identified bacteria in patient samples that resist all currently available antibiotic drugs.

Survival of the Fittest

The increased prevalence of antibiotic resistance is an outcome of evolution. Any population of organisms, bacteria included, naturally includes variants with unusual traits--in this case, the ability to withstand an antibiotic's attack on a microbe. When a person takes an antibiotic, the drug kills the defenseless bacteria, leaving behind--or "selecting," in biological terms--those that can resist it. These renegade bacteria then multiply, increasing their numbers a millionfold in a day, becoming the predominant microorganism.

The antibiotic does not technically cause the resistance, but allows it to happen by creating a situation where an already existing variant can flourish. "Whenever antibiotics are used, there is selective pressure for resistance to occur. It builds upon itself. More and more organisms develop resistance to more and more drugs," says Joe Cranston, Ph.D., director of the department of drug policy and standards at the American Medical Association in Chicago.

A patient can develop a drug-resistant infection either by contracting a resistant bug to begin with, or by having a resistant microbe emerge in the body once antibiotic treatment begins. Drug-resistant infections increase risk of death, and are often associated with prolonged hospital stays, and sometimes complications. These might necessitate removing part of a ravaged lung, or replacing a damaged heart valve.

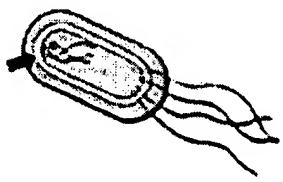
Bacterial Weaponry

Disease-causing microbes thwart antibiotics by interfering with their mechanism of action. For example, penicillin kills bacteria by attaching to their cell walls, then destroying a key part of the wall. The wall falls apart, and the bacterium dies. Resistant microbes, however, either alter their cell walls so penicillin can't bind or produce enzymes that dismantle the antibiotic.

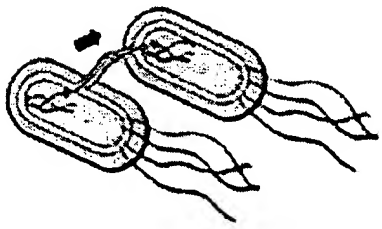
In another scenario, erythromycin attacks ribosomes, structures within a cell that enable it to make proteins. Resistant bacteria have slightly altered ribosomes to which the drug cannot bind. The ribosomal route is also how bacteria become resistant to the antibiotics tetracycline, streptomycin and gentamicin.

How Antibiotic Resistance Happens

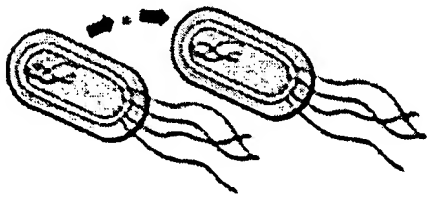
Antibiotic resistance results from gene action. Bacteria acquire genes conferring resistance in any of three ways.



In spontaneous DNA mutation, bacterial DNA (genetic material) may mutate (change) spontaneously (indicated by starburst). Drug-resistant tuberculosis arises this way.



In a form of microbial sex called transformation, one bacterium may take up DNA from another bacterium. Pencillin-resistant gonorrhea results from transformation.



Most frightening, however, is resistance acquired from a small circle of DNA called a plasmid, that can flit from one type of bacterium to another. A single plasmid can provide a slew of different resistances. In 1968, 12,500 people in Guatemala died in an epidemic of Shigella diarrhea. The microbe harbored a plasmid carrying resistances to four antibiotics!

A Vicious Cycle: More Infections and Antibiotic Overuse

Though bacterial antibiotic resistance is a natural phenomenon, societal factors also contribute to the problem. These factors include increased infection transmission, coupled with inappropriate antibiotic use.

More people are contracting infections. Sinusitis among adults is on the rise, as are ear infections in children. A report by CDC's Linda F. McCaig and James M. Hughes, M.D., in the Jan. 18, 1995, Journal of the American Medical Association, tracks antibiotic use in treating common illnesses. The report cites nearly 6 million antibiotic prescriptions for sinusitis in 1985, and nearly 13 million in 1992. Similarly, for middle ear infections, the numbers are 15 million prescriptions in 1985, and 23.6 million in 1992.

Causes for the increase in reported infections are diverse. Some studies correlate the doubling in doctor's office visits for ear infections for preschoolers between 1975 and 1990 to increased use of day-care facilities. Homelessness contributes to the spread of infection. Ironically, advances in modern medicine have made more people predisposed to infection. People on chemotherapy and transplant recipients taking drugs to suppress their immune function are at greater risk of infection.

"There are the number of immunocompromised patients, who wouldn't have survived in earlier times," says Cranston. "Radical procedures produce patients who are in difficult shape in the hospital, and are prone to nosocomial [hospital-acquired] infections. Also, the general aging of patients who live longer, get sicker, and die slower contributes to the problem," he adds.

Though some people clearly need to be treated with antibiotics, many experts are concerned about the inappropriate use of these powerful drugs. "Many consumers have an expectation that when they're ill, antibiotics are the answer. They put pressure on the physician to prescribe them. Most of the time the illness is viral, and antibiotics are not the answer. This large burden of antibiotics is certainly selecting resistant bacteria," says Blum.

Another much-publicized concern is use of antibiotics in livestock, where the drugs are used in well animals to prevent disease, and the animals are later slaughtered for food. "If an animal gets a bacterial

infection, growth is slowed and it doesn't put on weight as fast," says Joe Madden, Ph.D., strategic manager of microbiology at FDA's Center for Food Safety and Applied Nutrition. In addition, antibiotics are sometimes administered at low levels in feed for long durations to increase the rate of weight gain and improve the efficiency of converting animal feed to units of animal production.

FDA's Center for Veterinary Medicine limits the amount of antibiotic residue in poultry and other meats, and the U.S. Department of Agriculture monitors meats for drug residues. According to Margaret Miller, Ph.D., deputy division director at the Center for Veterinary Medicine, the residue limits for antimicrobial animal drugs are set low enough to ensure that the residues themselves do not select resistant bacteria in (human) gut flora.

FDA is investigating whether bacteria resistant to quinolone antibiotics can emerge in food animals and cause disease in humans. Although thorough cooking sharply reduces the likelihood of antibiotic-resistant bacteria surviving in a meat meal to infect a human, it could happen. Pathogens resistant to drugs other than fluoroquinolones have sporadically been reported to survive in a meat meal to infect a human. In 1983, for example, 18 people in four midwestern states developed multi-drug-resistant Salmonella food poisoning after eating beef from cows fed antibiotics. Eleven of the people were hospitalized, and one died.

A study conducted by Alain Cometta, M.D., and his colleagues at the Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland, and reported in the April 28, 1994, New England Journal of Medicine, showed that increase in antibiotic resistance parallels increase in antibiotic use in humans. They examined a large group of cancer patients given antibiotics called fluoroquinolones to prevent infection. The patients' white blood cell counts were very low as a result of their cancer treatment, leaving them open to infection.

Between 1983 and 1993, the percentage of such patients receiving antibiotics rose from 1.4 to 45. During those years, the researchers isolated Escherichia coli bacteria annually from the patients, and tested the microbes for resistance to five types of fluoroquinolones. Between 1983 and 1990, all 92 E. coli strains tested were easily killed by the antibiotics. But from 1991 to 1993, 11 of 40 tested strains (28 percent) were resistant to all five drugs.

Towards Solving the Problem

Antibiotic resistance is inevitable, say scientists, but there are measures we can take to slow it. Efforts are under way on several fronts--improving infection control, developing new antibiotics, and using drugs more appropriately.

Barbara E. Murray, M.D., of the University of Texas Medical School at Houston writes in the April 28, 1994, New England Journal of Medicine that simple improvements in public health measures can go a long way towards preventing infection. Such approaches include more frequent hand washing by health-care workers, quick identification and isolation of patients with drug-resistant infections, and improving sewage systems and water purity in developing nations.

Drug manufacturers are once again becoming interested in developing new antibiotics. These efforts have been spurred both by the appearance of new bacterial illnesses, such as Lyme disease and Legionnaire's disease, and resurgences of old foes, such as tuberculosis, due to drug resistance.

FDA is doing all it can to speed development and availability of new antibiotic drugs. "We can't identify new agents--that's the job of the pharmaceutical industry. But once they have identified a promising new

drug for resistant infections, what we can do is to meet with the company very early and help design the development plan and clinical trials," says Blum.

In addition, drugs in development can be used for patients with multi-drug-resistant infections on an "emergency IND (compassionate use)" basis, if the physician requests this of FDA, Blum adds. This is done for people with AIDS or cancer, for example.

No one really has a good idea of the extent of antibiotic resistance, because it hasn't been monitored in a coordinated fashion. "Each hospital monitors its own resistance, but there is no good national system to test for antibiotic resistance," says Blum.

This may soon change. CDC is encouraging local health officials to track resistance data, and the World Health Organization has initiated a global computer database for physicians to report outbreaks of drug-resistant bacterial infections.

Experts agree that antibiotics should be restricted to patients who can truly benefit from them--that is, people with bacterial infections. Already this is being done in the hospital setting, where the routine use of antibiotics to prevent infection in certain surgical patients is being reexamined.

"We have known since way back in the antibiotic era that these drugs have been used inappropriately in surgical prophylaxis [preventing infections in surgical patients]. But there is more success [in limiting antibiotic use] in hospital settings, where guidelines are established, than in the more typical outpatient settings," says Cranston.

Murray points out an example of antibiotic prophylaxis in the outpatient setting--children with recurrent ear infections given extended antibiotic prescriptions to prevent future infections. (See "Protecting Little Pitchers' Ears" in the December 1994 FDA Consumer.)

Another problem with antibiotic use is that patients often stop taking the drug too soon, because symptoms improve. However, this merely encourages resistant microbes to proliferate. The infection returns a few weeks later, and this time a different drug must be used to treat it.

Targeting TB

Stephen Weis and colleagues at the University of North Texas Health Science Center in Fort Worth reported in the April 28, 1994, New England Journal of Medicine on research they conducted in Tarrant County, Texas, that vividly illustrates how helping patients to take the full course of their medication can actually lower resistance rates. The subject--tuberculosis.

TB is an infection that has experienced spectacular ups and downs. Drugs were developed to treat it, complacency set in that it was beaten, and the disease resurged because patients stopped their medication too soon and infected others. Today, one in seven new TB cases is resistant to the two drugs most commonly used to treat it (isoniazid and rifampin), and 5 percent of these patients die.

In the Texas study, 407 patients from 1980 to 1986 were allowed to take their medication on their own. From 1986 until the end of 1992, 581 patients were closely followed, with nurses observing them take their pills. By the end of the study, the relapse rate--which reflects antibiotic resistance--fell from 20.9 to 5.5 percent. This trend is especially significant, the researchers note, because it occurred as risk factors for spreading TB--including AIDS, intravenous drug use, and homelessness--were increasing. The conclusion: Resistance can be slowed if patients take medications correctly.

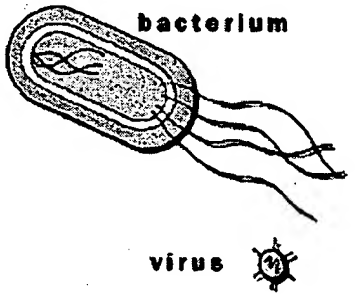
Narrowing the Spectrum

Appropriate prescribing also means that physicians use "narrow spectrum" antibiotics--those that target only a few bacterial types--whenever possible, so that resistances can be restricted. The only national survey of antibiotic prescribing practices of office physicians, conducted by the National Center for Health Statistics, finds that the number of prescriptions has not risen appreciably from 1980 to 1992, but there has been a shift to using costlier, broader spectrum agents. This prescribing trend heightens the resistance problem, write McCaig and Hughes, because more diverse bacteria are being exposed to antibiotics.

One way FDA can help physicians choose narrower spectrum antibiotics is to ensure that labeling keeps up with evolving bacterial resistances. Blum hopes that the surveillance information on emerging antibiotic resistances from CDC will enable FDA to require that product labels be updated with the most current surveillance information.

Many of us have come to take antibiotics for granted. A child develops strep throat or an ear infection, and soon a bottle of "pink medicine" makes everything better. An adult suffers a sinus headache, and antibiotic pills quickly control it. But infections can and do still kill. Because of a complex combination of factors, serious infections may be on the rise. While awaiting the next "wonder drug," we must appreciate, and use correctly, the ones that we already have.

Big Difference



If this bacterium could be shown four times bigger, it would be the right relative size to the virus beneath it. (Both are microscopic and are shown many times larger than life.)

Although bacteria are single-celled organisms, viruses are far simpler, consisting of one type of biochemical (a nucleic acid, such as DNA or RNA) wrapped in another (protein). Most biologists do not consider viruses to be living things, but instead, infectious particles. Antibiotic drugs attack bacteria, *not* viruses.

The Greatest Fear--Vancomycin Resistance

When microbes began resisting penicillin, medical researchers fought back with chemical cousins, such as methicillin and oxacillin. By 1953, the antibiotic armamentarium included chloramphenicol, neomycin, terramycin, tetracycline, and cephalosporins. But today, researchers fear that we may be nearing an end to the seemingly endless flow of antimicrobial drugs.

At the center of current concern is the antibiotic vancomycin, which for many infections is literally the drug of "last resort," says Michael Blum, M.D., medical officer in FDA's division of anti-infective drug products. Some hospital-acquired staph infections are resistant to all antibiotics except vancomycin.

Now vancomycin resistance has turned up in another common hospital bug, enterococcus. And since bacteria swap resistance genes like teenagers swap T-shirts, it is only a matter of time, many

microbiologists believe, until vancomycin-resistant staph infections appear. "Staph aureus may pick up vancomycin resistance from enterococci, which are found in the normal human gut," says Madden. And the speed with which vancomycin resistance has spread through enterococci has prompted researchers to use the word "crisis" when discussing the possibility of vancomycin-resistant staph.

Vancomycin-resistant enterococci were first reported in England and France in 1987, and appeared in one New York City hospital in 1989. By 1991, 38 hospitals in the United States reported the bug. By 1993, 14 percent of patients with enterococcus in intensive-care units in some hospitals had vancomycin-resistant strains, a 20-fold increase from 1987. A frightening report came in 1992, when a British researcher observed a transfer of a vancomycin-resistant gene from enterococcus to Staph aureus in the laboratory. Alarmed, the researcher immediately destroyed the bacteria.

Ricki Lewis is a geneticist and textbook author.

FDA HOME PAGE TABLE OF CONTENTS

FDA Consumer magazine (September 1995)